IN THE UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF CALIFORNIA SAN FRANCISCO DIVISION

FLUIDIGM CORPORATION,

a Delaware Corporation; and

FLUIDIGM CANADA INC.,

a foreign corporation,

Plaintiff

v.

IONPATH, INC.,

a Delaware Corporation,

Defendant.

Case No. 3: 19-cv-05639-WHA

Honorable William H. Alsup

INDEPENDENT EXPERT REPORT OF THOMAS F. KELLY

1. I have been retained by counsel for Fluidigm Corporation and Fluidigm Canada, Inc., (individually and collectively "Fluidigm") to provide my independent expert opinion regarding claim construction and specifically what a person of ordinary skill in the art of mass spectrometry at the time of the inventions and/or applications for United States Patent Nos. 10,180,386 (the "'386 Patent") and 10,436,698 (the "'698 Patent") (collectively, the "Fluidigm Patents") would understand certain claim terms and limitations in those patents to mean.

2. This is my Independent Expert Report.

3. In formulating my opinions, I reviewed and considered the documents and materials identified in this Report. My opinions are also based on my education, training, research, knowledge and professional experience. If asked to testify regarding my opinions and bases therefore, I am prepared to do so.

A SUMMARY OF MY QUALIFICATIONS

4. I received a Ph.D. in Materials Science from the Massachusetts Institute of Technology, Cambridge Massachusetts, under Professors John B. Vander Sande and Morris Cohen. I received an undergraduate degree from Northeastern University, in Boston, Massachusetts, in Mechanical Engineering (with highest honors).

5. Before entering industry, I worked for approximately 18 years as a Professor, Associate Professor, and Assistant Professor, at the University of Wisconsin, Madison WI, in the Department of Materials Science and Engineering and also served as the Director of the Materials Science Center at the University, a heavily used instrumentation center including, among other technologies, transmission electron microscopy, scanning electron microscopy, x-ray diffraction, and various surface analysis instruments. My research included analytical electron microscopy and atom probe tomography.

6. I have been involved in the development of atomic and molecular detection technologies for approximately 30 years including as the Founder, Chief Executive Officer, and Chief Technical Officer, of Imago Scientific Instruments Corporation, which developed and commercialized atom probe tomography instruments.

7. Imago Scientific was acquired by Ametek, Inc., in 2010. At that time, I became the Division Vice President for Innovation and New Technologies, as well as the Chair of Scientific Council and Chair of Materials Analysis Division Committee on Innovation and New Technologies, at CAMECA Instruments, Inc., a business unit of Ametek, Inc. At CAMECA Instruments, I was responsible for, among other things, all innovation on all product lines and driving innovation in the Materials Analysis Division.

8. I resigned from CAMECA in August 2018 so that I could start Steam Instruments, Inc., which is developing new detector technology and mass spectrometry instruments for biomolecules. I am the Founder and currently the Chief Executive Officer of Steam Instruments.

9. I am and have been involved in numerous professional societies and activities including, for example, as Fellow of the Microscopy Society of America, Fellow and President of the Microanalysis Society, Fellow and President of the International Field Emission Society, and on the Advisory Board for the Oak Ridge National Laboratory Center for Nanophase Materials Science, among others.

10. I have received numerous R&D and other research awards, and have over 230 publications and 19 patent applications with 12 issued patents.

11. Additional information on my qualifications, background and experience can be found in my curriculum vitae, attached as Exhibit 1 to this Independent Expert Report, which provides a list of my positions, professional activities and society memberships, articles, courses, seminars, presentations, and patents.

12. Among other experience I have with secondary-ion mass spectrometry ("SIMS"), while serving as Director of the Materials Science Center at UW Madison, I was responsible for oversight and direction for a dynamic SIMS (CAMECA 3f). While at CAMECA, I was responsible for innovation on all instrumentation which included, among other instruments, the standard dynamic SIMS (the current model was then the 7f), the large-magnet dynamic SIMS (models IMS 1280 and IMS 1300 HR^3), and the NS50L nanoSIMS.

COMPENSATION

13. I am being compensated at a rate of $400/hour. My compensation is not dependent on the nature of my opinions or the outcome of this case.

PRIOR TESTIMONY

14. I have not previously provided expert support in any patent litigation cases, or testified as an expert at trial or deposition within the preceding four years.

INFORMATION CONSIDERED

15. In addition to my background, including my education and experience, my opinions in this Independent Expert Report are based on my review of:

i. The '386 and '698 Patents;

ii. The file histories of the '386 and '698 Patents;

iii. Joint Claim Construction and Prehearing Statement, dated June 1, 2020, including Exhibit 1 setting forth Fluidigm and IONpath proposed constructions and support

iv. Methods for Generating Protein Molecular Ions in TOF-SIMS by McArthur, 2004

v. Glow Discharge Mass Spectrometry, Methods by Annemie Bogaerts, 1999

vi. Atomic Mass Spectrometry by Blades, 1994

vii. Practical Guide to ICP-MS by Thomas, 2004

viii. A Mass Spectrometry Primer for Mass Spectrometry Imaging by Rubakhin and Sweedler, 2010

ix. Atomic and Molecular Imaging at the Single-Cell Level with TOF-SIMS by Colliver, 1997

x. U.S. PG-Pub No. 2002/0086441 to Baranov et al., 2002

xi. A Beginner's Guide to ICP-MS, Parts I-XI, by Thomas, 2001-2002

xii. MIBI-TOF: A Multiplexed Imaging Platform Relates Cellular Phenotypes and Tissue Structure by Keren et al., 2019.

xiii. Local Electrode Probe Tomography: A User's Guide, by Larson et al., Springer, 2013.

TECHNOLOGY BACKGROUND AND TUTORIAL

16. The '386 and '698 Patents are directed to multiplexed analysis of cell samples at the single cell level, using mass spectrometry techniques. In the multiplexed analysis, a plurality of different analytes in a sample are identified by providing a plurality of different tagged antibodies that are each specific for the different analytes, which may be, for example, different proteins or other biomarkers in the sample. For example, the plurality of different tagged antibodies may be specific for certain proteins or other biomarkers that are of interest to a researcher or a physician. As each type of protein or other biomarker has a different chemical structure, a specific antibody may be selected for that structure, and each particular antibody employed will only bind to that corresponding protein.

17. The ability to evaluate such multiplex information at the cellular level has been a transformative breakthrough for medical research, allowing for the identification of interactions and relationships between multiple different proteins or other biomarkers in or on the cells, and providing for the multiplexed profiling of cells to determine correlations between the presence and/or relative levels of multiple different biomarkers and disease states. Examples of research and/or diagnostic areas where multiplexed single cell analysis technique has been implemented to make new discoveries including, for example, cancer research and immuno-oncology,

immunology, immunophenotyping, infectious disease/microbiology studies (including studies on COVID-19), liquid biopsy, neurology, oncology, and stem cell research.

18. To facilitate multiplexing in single cell analysis, each antibody is tagged with an elemental tag comprising a lanthanide or noble metal. The elemental tags thus include an element (lanthanide or noble metal), or an isotope of an element, that can provide a distinguishable signal for the specific antibody. The use of elemental tags comprising lanthanides and/or noble metals, including their many isotopes, allows for multiplexing analysis because each has a different molecular weight distinguishable by mass spectrometry. In other words, the protein or biomarker of interest is bound by an antibody which in turn is labeled or tagged with a specific elemental tag. When the elemental tag is detected by mass spectrometry, it provides a signal indicating that the protein or biomarker of interest was present in or on the cell. For purposes of illustration, Figure 1 below[1] shows an example of such an elemental tag, in this case having lanthanide atoms (Ln) conjugated via a polymer chain to an antibody.

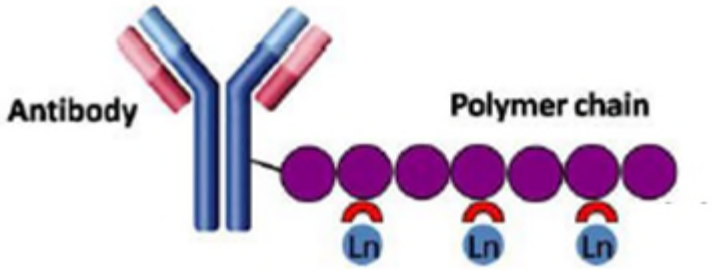


Figure 1

[1] Figures 1- 3 are more recent schematics created after the 2004 filing date of the '386 and '698 Patents, but are representative of the invention as claimed.

19. Importantly, the multiplexed analysis described in the '386 and '698 Patents is performed by sequential analysis of single cells, such that information about the multiple analytes that may be present in or on different cells can be determined at the cellular level. As described by the claims of the '386 and '698 Patents, the sequential analysis of the single cells involves vaporizing, atomizing, and ionizing the multiple elemental tags from first and second cells. As described below, vaporizing and ionizing is required because the elemental tags are detected by mass spectrometry. Figure 2 below illustrates an example of multiplexed analysis of cells in a tissue or cell line sample,[2] where a laser ablation technique is used vaporize material from different laser ablation spots corresponding to different cells on the sample.

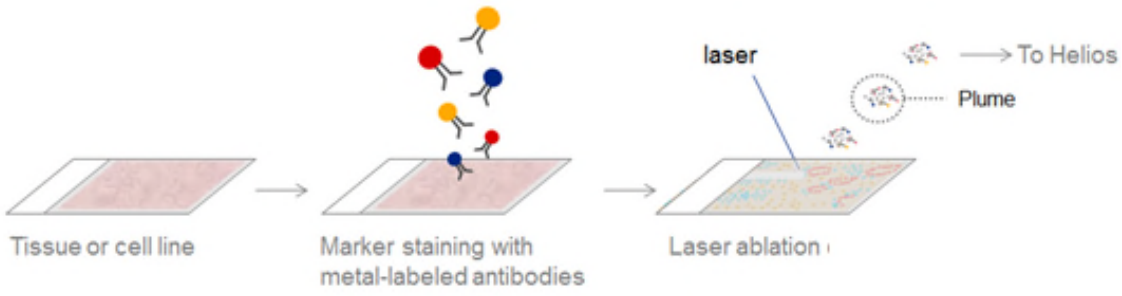


Figure 2

20. A transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell is detected using mass spectrometry, and a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the second cell is detected using mass spectrometry, with the transient signal associated with the first cell and the

[2] In a "staining" process, the elemental tags conjugated to the antibodies are introduced to the sample, such that the conjugated antibodies become bound to the analyte of interest in the sample (i.e. the antibodies bind to analyte in the sample for which they are specific).

transient signal of the second cell being detected sequentially. Figure 3 below shows an example of detection via mass spectrometry, using a time-of-flight (TOF) detector that separates ions in a transient signal according to their mass, to distinguish ions having different masses from one another.

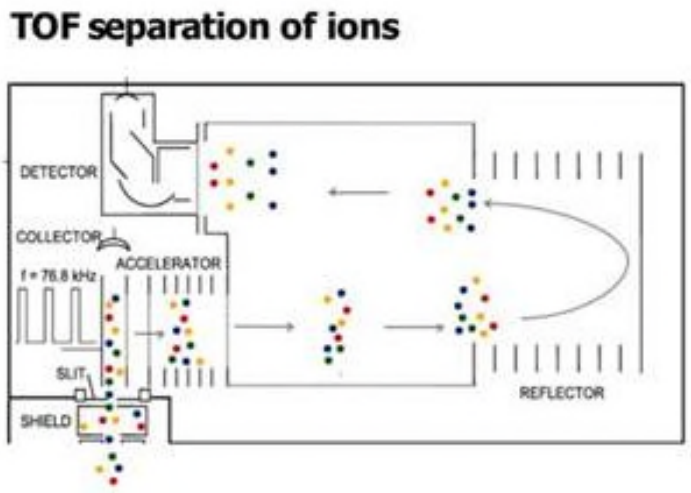


Figure 3

21. The elemental composition (in '386) or the lanthanides and/or noble metals (in '698) of the first and second cells are thus detected via this multiplexing single cell analysis technique. That is, by providing for systems and methods that allow for the sequential detection of the transient signals of the multiple vaporized, atomized and ionized elemental tags, with the transient signals each being associated with either the first or second cell in the sequential detection, multiplexed analysis of analyte at the individual cell level is possible. Atomizing the elemental tag is required because it is the individual ionized lanthanide or noble metal atoms that are detected by mass spectrometry.

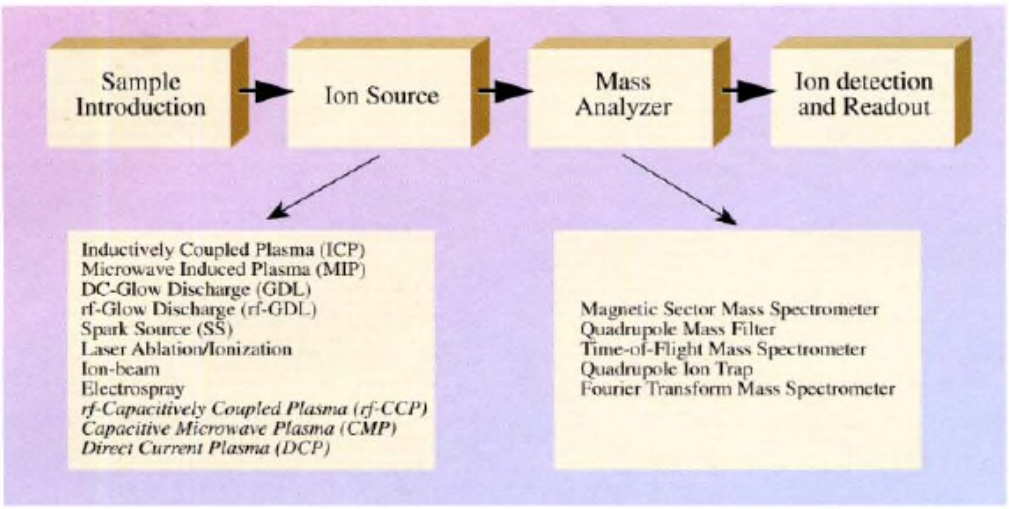
Mass Spectrometry

22. Generally speaking, mass spectrometry involves the detection of the mass of an ionized element or other substance, to identify moieties of interest in a sample. *See*, e.g., Introduction to "A Mass Spectrometry Primer for Mass Spectrometry Imaging," Rubakhin & Sweedler, *Methods Mol Biol.* 2010; 656; 21-49 (hereinafter referred to as "Rubakhin").

23. Unless the element or substance of interest is already in a gas phase, it must be vaporized from a solid or liquid phase and ionized to provide an ionic form suitable for detection by a mass analyzer/detector (*see, e.g.*, Rubakhin page 3; "analytes need to be vaporized from a solid or liquid phase, ionized, and transferred into the vacuum system of the mass analyzer"). That is because the detector of the mass analyzer is detecting individual elements or molecules in ionized form. "Vaporization" can be achieved by a variety of different processes, including heating of the sample, exposure of the sample to a high electric field, applying laser irradiation, bombardment with ions, and other methods that are capable of imparting energy to the sample to liberate the material to be detected from the sample (*see, e.g.*, Rubakhin page 3; "[v]aporization can be achieved by a variety of techniques, including heating the samples, exposing them to a high electric field ... and/or via bombardment with fast atoms, or atomic or molecular ions").

24. As such, the two key steps of mass spectrometry are vaporizing and ionizing the element or substance of interest and detecting the resulting ionized element or substance. In addition, if an individual ionized element is being detected, then the elemental tag must be atomized such that the individual ionized element can be

detected separately. As shown in the chart below, and known to people in the field, a variety of ion sources can be used to vaporize and ionize the element or substance of interest and a variety of mass analyzers or detectors can be used to detect the resulting ionized element or substance. (*See*, page 13A of "Atomic Mass Spectrometry," M.W. Blades, *Applied Spectroscopy*, 1994: Vol. 48; Number 11 (hereinafter referred to as "Blades")).



Ion Sources

25. By 2004, some commonly used techniques for the generation of ions from a sample of interest included: (a) inductively coupled plasmas (ICP); (b) Microwave Induced Plasma (MIP); (c) DC- or RF- Glow Discharge (GD); (d) Spark Source (SS); (e) Laser Ablation/Ionization; (f) Ion-Beam (e.g., generation of secondary ions by directing an ion beam onto a sample); and (g) Electrospray, among others (*see, e.g.*, page 13A of "Blades").

26. For example, in Inductively Coupled Plasma Mass Spectrometry (“ICP-MS”), which is one apparatus described in the '386 and '698 Patents (*see*, e.g., '386 Patent, 13:12-39), material to be analyzed is introduced into an inductively coupled plasma chamber where energized plasma species (e.g. argon plasma ions and free electrons) break up or atomize the material, and then generate ions from the atomic components. As material introduced into the ICP chamber moves further into the plasma, the material changes first into a gaseous form and then into ground state atoms, with the final process of conversion of the atoms to ions being achieved by collisions of the energetic plasma species (the free electrons in the plasma and also to a lesser extent the plasma gas ions) with the ground state atoms (*see, e.g.,* "Spectroscopy Tutorial: A Beginner's Guide to ICP-MS" by Robert Thomas, 2001-2002, pages 29-30 in Part III (hereinafter referred to as "Thomas 2001-2002"; and "Practical Guide to ICP-MS" by Robert Thomas, pages 29-30 in Chapter 4, hereinafter referred to as "Thomas 2004")). The ionized atomic species are then directed to a mass analyzer/detector for analysis. To illustrate, referring to FIG. 2 of the '386 and '698 Patents below, ionized atomic species formed in the device 104 for vaporizing, atomizing and ionizing the elemental tags (e.g., an ICP chamber according to one embodiment in the '386 and '698 Patents) are directed to spectrometer 106, which may be, for example, a TOF detector 126 (*see, e.g.*, '386: 7: 46-8:20).

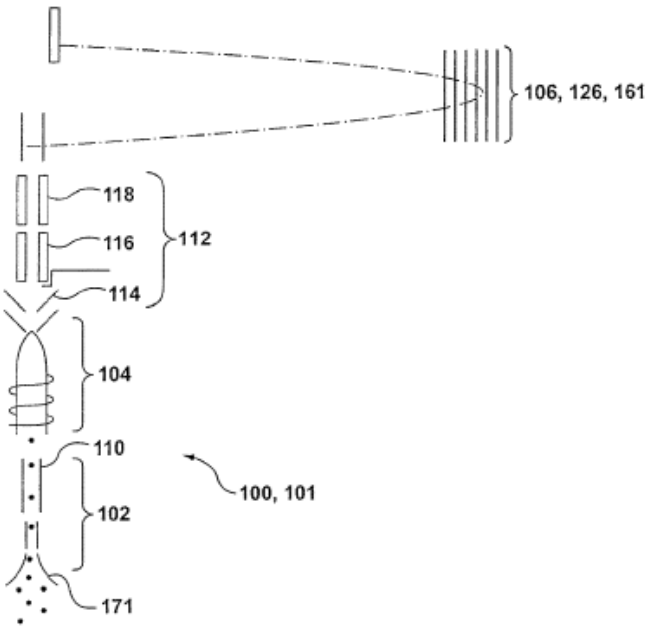


FIG. 2

27. Schematically, the vaporization, atomization and ionization process performed by the ICP technique described in the patent to create ions from material introduced in droplet form is depicted below (*see* Figure 5 on page 29, Part III of Thomas 2001-2002):

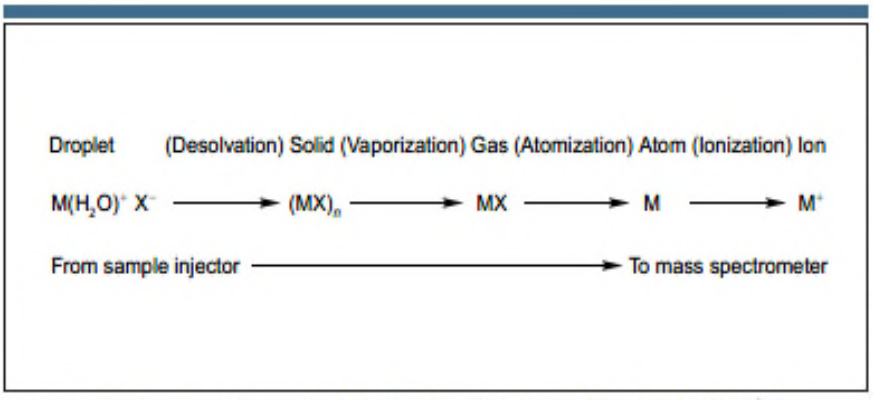


Figure 5. Mechanism of conversion of a droplet to a positive ion in the ICP.

28. Glow discharge is one of many known techniques among those specifically identified in the '386 and '698 Patents for performing vaporization, atomization, ionization of a sample (*see, e.g.,* '386 Patent, 6:59-7:2). In the glow discharge technique, a plasma is formed at a very low pressure (e.g., 1 torr), by applying a potential difference between two electrodes sufficient to create a gas breakdown and split the gas into positive ions and electrons (*see, e.g.,* "Glow Discharge Mass Spectrometry, Methods" by Annemie Bogaerts, 1999 (hereinafter referred to as "Bogaerts"), page 669). The plasma ions are accelerated towards a sample to be analyzed, with the kinetic energy of the ions being transferred to the sample on impact, and thereby causing surface material to be ejected from the sample surface -- a phenomenon often referred to as “sputtering”. The material released from the sample by this sputtering process enters the plasma where the material is ionized, and the ions can be detected by a mass analyzer/detector (*see, e.g.,* Bogaerts, page 669, "[t]he use of glow discharge as an ion source for mass spectrometry is based on the phenomenon of sputtering": Blades, page 16A, "[t]he impinging ion ... penetrates to a depth of a few angstroms where its kinetic energy can cause surface atoms to be ejected ... a phenomenon called sputtering”).

29. In this technique, the glow discharge plasma ions serve as "primary ions" that sputter material from the sample, to facilitate the generation of "secondary ions" corresponding to the ionized material that has been liberated from the sample. For example, the figure below shows a schematic example of a glow discharge device, where argon ions from the plasma (i.e. "primary ions") sputter the sample at the cathode, resulting in ejection of material M^O and ionization M^+ thereof (i.e. "secondary

ions"), followed by travel of these secondary ions to the mass spectrometer (*see* page 670 of Bogaerts).

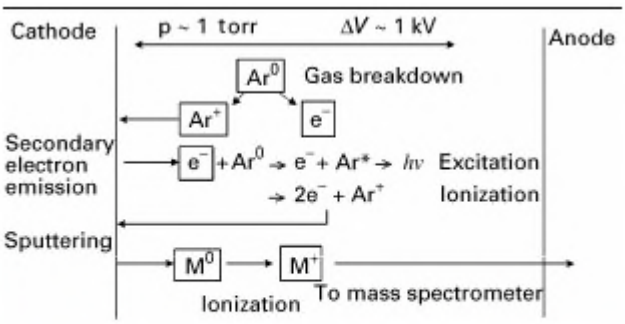


Figure 1 Schematic of the basic processes in a glow discharge.

30. Another sputtering technique for vaporizing, atomizing and ionizing a sample that was long known, and was available in 2004, was Secondary Ion Mass Spectrometry "SIMS" (*see* Blades, page 13A). In the SIMS technique, the tool for sputtering the sample includes a beam of fast-moving ions ("primary ions"), which can be created by extracting the ions generated by a plasma (*see, e.g.*, page 1375 of "A Structure Tumor-Immune Microenvironment in Triple Negative Breast Cancer Revealed by Multiplexed Ion Beam Imaging," Keren et al.; 2019; Cell; 174; 1373-1387 (hereinafter referred to as "Keren"): "... rasterizing oxygen duoplasmatron primary ion beam"). The fast moving primary ions are directed at a sample, and transfer kinetic energy to the sample surface upon impact, much as in the glow discharge technique described above, which causes material to be released from the sample surface -- "vaporized" -- in the form of gas phase neutrals and ions (referred to as "secondary ions"). The secondary ions released from the sample are transported to a mass

analyzer/detector for analysis. (*See, e.g.*, Blades page 16A; Rubakhin, Section 2.2.1.1, "The bombardment process results in formation of gas phase neutrals, ions ..."; "Methods for Generating Protein Molecular Ions in TOF-SIMS" by McArthur et al., Langmuir 2004, 20, 3704-3709 (hereinafter referred to as "McArthur"), Abstract, "The vaporization process used in TOF-SIMS ..."; "Atomic and Molecular Imaging at the Single-Cell Level with TOF-SIMS" by Colliver et al., Anal. Chem 1997, 69, 2225-2231 (hereinafter referred to as "Colliver"), page 2225 "SIMS can now be used to investigate ... important biological molecules ... [that] desorb directly into the gas phase using energetic ion beams.")

31. An example of a SIMS device known and available at the time of filing of the '386 and '698 Patents is depicted below, which shows a primary ion beam directed onto a sample, with the secondary ions that have been vaporized from the sample being directed to a mass spectrometer for detection (Blades, page 17A and Fig. 4).

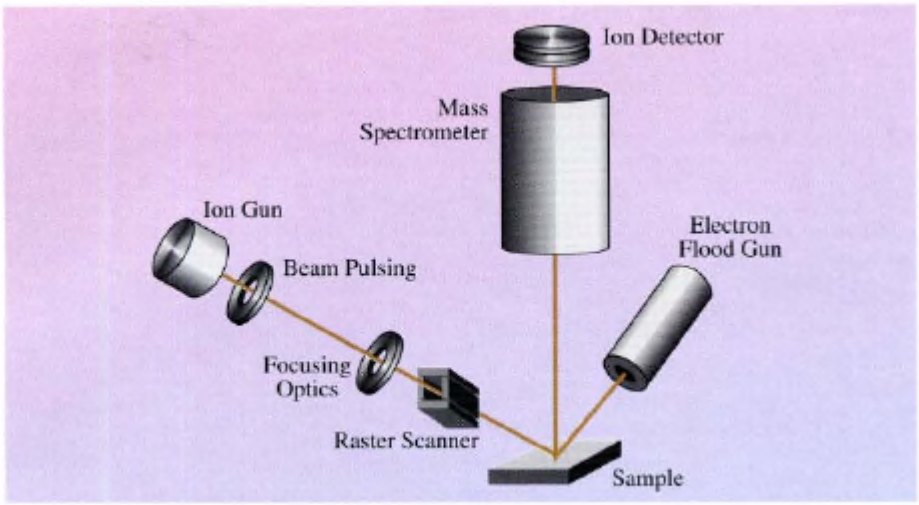
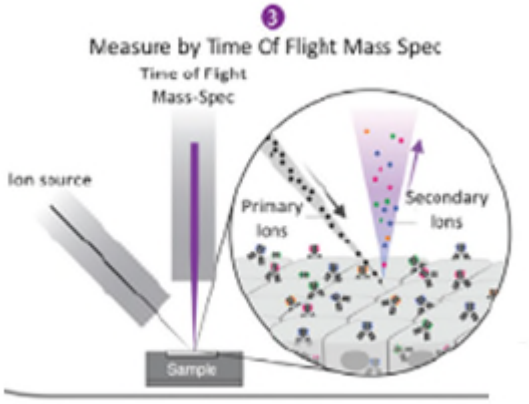


FIG. 4. A schematic diagram of a secondary ion mass spectrometer. The electron flood gun is used to maintain charge balance at the sample.

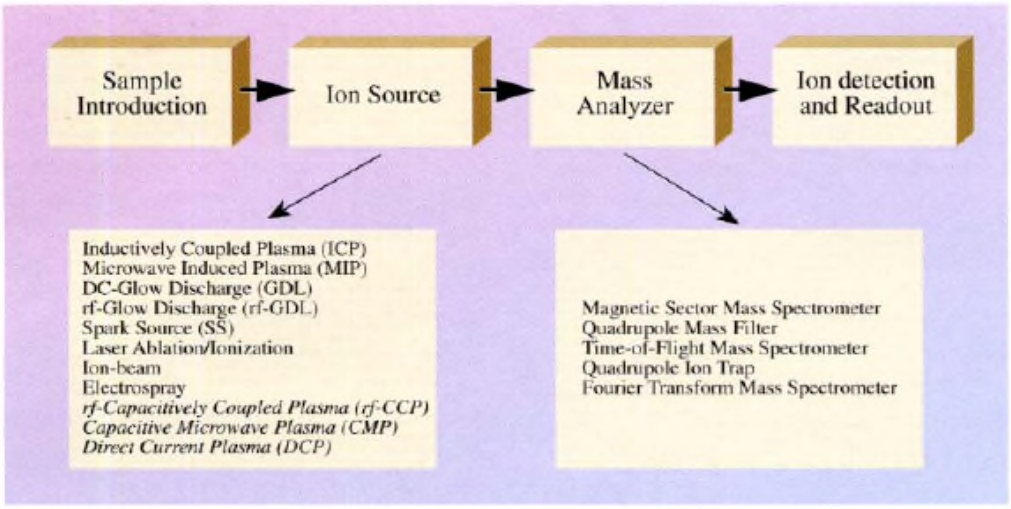
32. Another version of the SIMS method exhibiting vaporization, atomization, and ionization via sputtering with an ion beam, and the use of a time of flight mass spectrometer ("TOF-MS"), is depicted below (Keren, page 1374):



33. In summary, while a number of different techniques (ICP, glow discharge, SIMS, and other techniques) were known to persons of ordinary skill in the art at the time of filing of the '386 and '698 patents for creating ions from a sample, they all apply energy to vaporize the material of interest from a solid or liquid phase of the sample, in order to provide the material in an ionized form suitable for detection by a mass analyzer/mass spectrometer (*see*, Rubakhin Section, 2.2.1 Ion Sources "Unless originally in the gas phase, analytes need to be vaporized from a solid or liquid phase"). In addition, at least the glow discharge technique and the SIMS technique both used a "sputtering" mechanism as a part of a process for forming ions ("secondary ions") for detection by a mass analyzer/spectrometer, with a main difference between the two techniques primarily being in how the "primary ions" used for the sputtering were created (i.e. from a glow discharge plasma, or ion beam in SIMS).

Mass Analyzer/Detector

34. In addition to an ion source, the other critical feature of mass spectrometry is a mass analyzer (Blades, page 13A, Fig. 1, 1994).



35. Mass analyzers known and available at the time of filing of the '386 and '698 patents included, for example, magnetic sector mass spectrometers, quadrupole mass filters, time-of-flight mass spectrometers, quadrupole ion traps, and Fourier transform mass spectrometers. *Id*.

36. One way to measure mass is to observe the acceleration of an ion from rest due to an electric field. Heavier ions take a longer time to fly from the starting point (specimen) to the end point (detector). Thus, the flight time can be related directly to the mass of the ion. Detectors for time of flight mass spectrometry ("TOF MS") are configured to report the arrival time of the ion. To determine a time of flight, there must be a way to determine when the ion left the specimen. This can be accomplished

by pulsing the ion extraction event. As was known at the time, this can be done with a laser pulse (laser desorption/ionization ("LDI")), an ion pulse (using SIMS), or other methods then known to those skilled in the field. In my opinion, the identification and use of TOF MS in the '368 and '698 Patents discloses and teaches to those skilled in the art that the inventions include employing LDI and SIMS devices. Flight times are usually in the microsecond range which means that to measure TOF, it is necessary to determine the ion departure time to about one nanosecond to have good timing precision, and therefore good mass precision. These terms are referred to as timing resolution and mass resolution, respectively. Modern electronics can measure the flight time to a small fraction of a nanosecond. It is typical that a good TOF MS can measure the mass (actually, m/z, where z is the charge state) to a precision of a hundredth of an atomic mass unit (Dalton). A TOF mass spectrum from an atom probe tomograph of an aluminum alloy is shown in Figure 1 below.

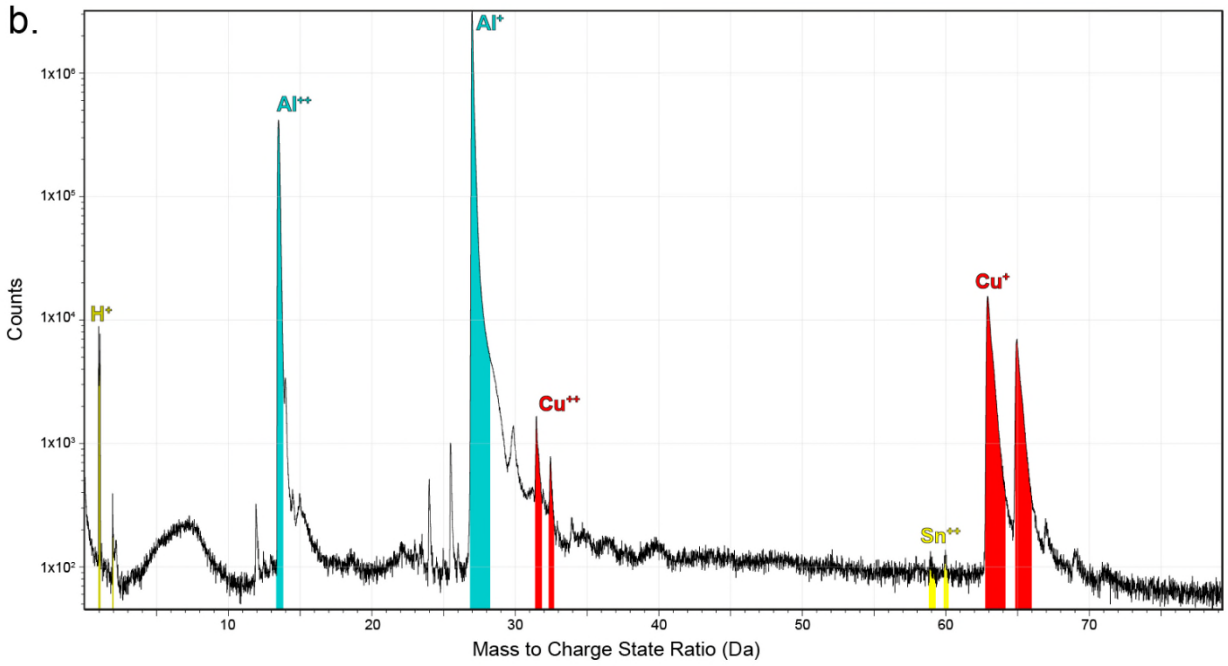


Figure 1

37. The Math. The gain in potential energy that an ion receives from an accelerating voltage ("V") is:

1. **P.E. = z e V**

where P.E. is the potential energy, z is the charge state, and e is the charge on an electron. This gain in potential energy is converted entirely to kinetic energy,

2. **K.E. = ½ m $v^2$2**

So that,

3. **z e V = ½ m v^2**

Since the flight is almost at constant speed, we can assume that

4. **v=constant = L/t**

where L is the flight path length and t is the time of flight. Equation 4 can be solved as

5. **m/z = 2 e V t^2/L^2**

38. Thus, measuring the time of flight, t, gives the mass-to-charge-state ratio as shown in Figure 1. The nominal configuration of a straight flight path ToF MS is shown in Figure 2.

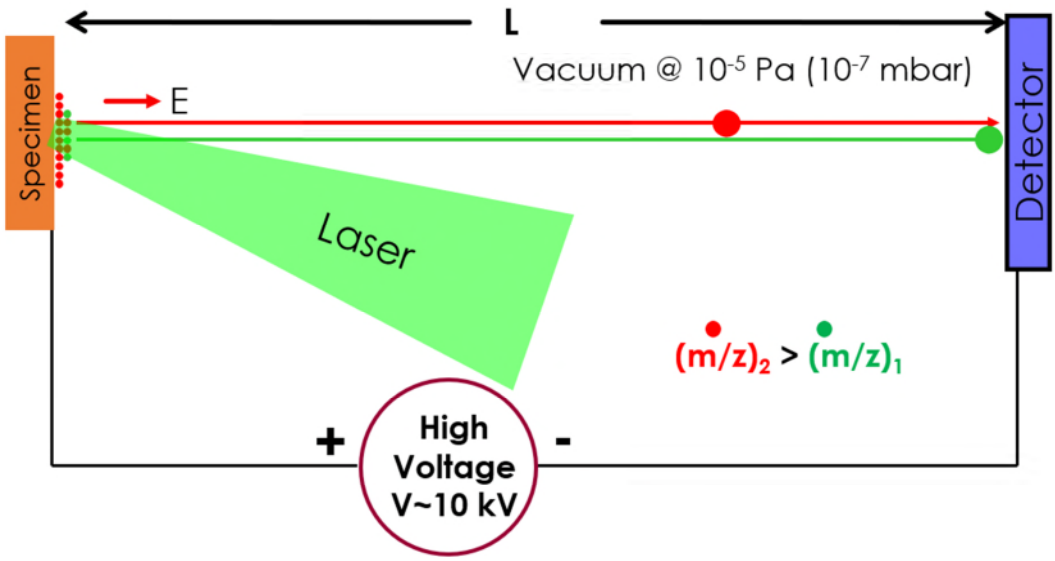


Figure 2

39. An exemplary schematic of ion separation using TOF is illustrated below, showing three ions of different mass-to-charge ratios being accelerated and arriving at a detector at different times, with the lightest mass ion arriving first, the medium mass ion arriving second, and the heaviest mass ion arriving last (*see, e.g.*, Thomas 2001-2002, page 36, Figure 1, of Part VIII):

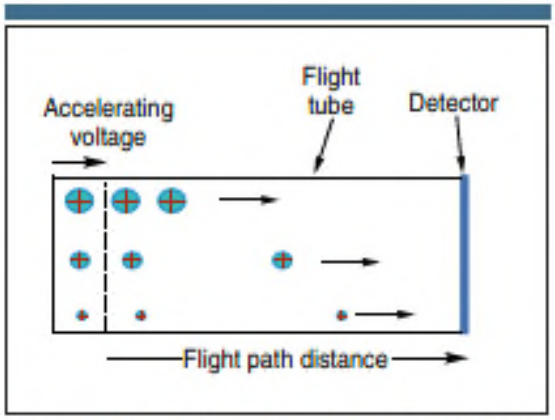


Figure 1. Principles of ion detection using TOF technology, showing separation of three masses in the time domain.

40. The TOF technique allows for separation of ions based on their different masses, such that ions having a lighter mass reach the detector before ions having heavier masses, allowing the ions to be distinguished from one another. Other techniques for the separation of ions based on their differing masses can also be provided, such as magnetic sector techniques that use a magnetic field to curve trajectories of ions in relation to the magnitude of the ion's mass-to-charge ratio, for example (see, e.g., Rubhakin, Section 2.2.2.3).

41. As a result of the ability to differentiate between ions of different mass-to-charge ratios (or in the case of ions having the same ionic charge z, the ability to differentiate between ions of different masses), mass analyzers/detectors used in mass spectrometry techniques are capable of analyzing a variety of different ionized materials, including ions formed from samples in a liquid or solid state.

Elemental Tags

42. The '386 and '698 Patents provide the ability to multiplex -- simultaneously identify multiple different analytes in a sample -- by using elemental tags that act as labels for the different analytes and which provide a distinguishable signal of the presence of analyte or analyte complex with which the elemental tags are associated (*see, e.g.*, '386 Patent, 5:52-67). For example, multiplexing can provide for the simultaneous identification of multiple different proteins or biomarkers in a sample. The elemental tags in turn contain an element, or an isotope of an element, that provides the distinguishable signal (*see, e.g.*, '386 Patent, 5:52-67).

43. Specifically, in claim 1 of each of the '386 and '698 Patents, the elemental tags comprise "a lanthanide or noble metal," including distinct isotopes thereof, that provides the distinguishable signal corresponding to each of the plurality of tagged antibodies that are tagged with the elemental tags, and which are specific for different analyte in the sample. Stated differently, multiple different analytes and/or biomarkers in a sample are each tagged with a unique elemental tag (via antibodies specific for said analyte) such that the presence of each analyte can be determined by detection of its distinct elemental tag.

44. The multiple elemental tags are vaporized, atomized and ionized to liberate the elemental tags from the sample and provide the elemental tags in their ionized atomic form, such as by a suitable vaporization, atomization and ionization technique (e.g. ICP, graphite furnace, capacitively coupled plasma, glow discharge, SIMS, or other suitable technique). For elemental tags comprising lanthanides or noble metals, the ionized form of the lanthanide or noble metal atoms themselves are formed as a result

of vaporization, atomization and ionization process. As part of this process, the lanthanides or noble metals which were attached to an antibody have been separated into their atomic components — that is, they have been atomized. The lanthanides or noble metals in ionized atomic form are detected in the claimed inventions using mass spectrometry to distinguish between lanthanides or noble metals of different mass by using ToF MS. In other words, the detection of the unique lanthanides and/or noble metals provide information about the presence in the sample of the analyte they were provided to tag.

Isotopes

45. The elemental tags comprising the lanthanide or noble metal recited in claim 1 of each of the '386 and '698 Patents can, in my opinion, include any of the lanthanide series of chemical elements, any of the noble metal chemical elements, as well as any isotopes thereof (*see, e.g.*, '386 Patent, 5:52-67). For example, the lanthanide series of chemical elements includes Lanthanum (La), Cerium (Ce), Praseodynium (Pr), Neodynium (Nd), Prometheum (Pm), Samarium (Sm), Europium (Eu), Gadolinium (Gd), Terbium (Tb), Dysprosium (Dy), Holmium (Ho), Erbium (Er), Thulium (Tm), Ytterbium (Yb) and Lutetium (Lu).

46. Multiplexing can be enabled using different elemental tags each comprising a different lanthanide element, such as a first elemental tag comprising Europium (lanthanide chemical element number 63, average atomic mass of 151.964 amu) and a second elemental tag comprising Gadolinium (lanthanide chemical element number 64, average atomic mass of 157.25 amu) (*see, e.g.*, '386 Patent, 10:5-9). Since the element

Gadolinium has a different mass than Europium, these element tags can be distinguished from one another using mass spectrometry techniques. In addition, multiplexing can also be provided by including distinct isotopes of the lanthanide and/or noble metals, where the distinct isotopes are isotopes of an element that has a distinguishable mass from other isotopes, of the same or other element, used as tags in the sample (*see, e.g.,* '386 Patent: 5:52-57). Ideally, the lanthanides and/or noble metals that are used are also of relatively low natural abundance, to reduce the likelihood of detecting "endogenous" species (species naturally occurring in a sample, not elemental tags), which would not be indicative of the presence of analyte, but rather of the presence of the endogenous material per se, and so could interfere with analysis of the analyte in the sample.

47. While different chemical elements have different masses that are distinguishable from one another, due to the combined weights of the protons, neutrons and electrons making up each chemical element, each chemical element can also exist in multiple different isotopic forms according to varying numbers of neutrons present in the nucleus of each. That is, different isotopes of the same element have the same number of protons and electrons, but differ in the number of neutrons present for each isotope, which results in a small -- but detectable -- difference in mass between different isotopes of a same chemical element. Some examples of isotopes detectable by ICP-MS are below (*see*, Thomas 2001-2002, page 43 of part IX).

Table I. Typical detection limits (in ppb) achievable with a hexapole-based collision cell ICP-MS system (4).

Element	Isotope	Elemental Sensitivity (cps/[μg/mL])	Detection Limit (ppb)
Be	9	6.9×10^7	0.0077
Mg	24	1.3×10^8	0.028
Ca	40	2.8×10^8	0.07
V	51	1.7×10^8	0.0009
Cr	52	2.4×10^8	0.0007
Mn	55	3.4×10^8	0.0017
Fe	56	3.0×10^8	0.017
Co	59	2.7×10^8	0.0007
Ni	60	2.1×10^8	0.016
Cu	63	1.9×10^8	0.003
Zn	68	1.1×10^8	0.008
Sr	88	4.9×10^8	0.0003
Ag	107	3.5×10^8	0.0003
Cd	114	2.4×10^8	0.0004
Te	128	1.3×10^8	0.009
Ba	138	5.9×10^8	0.0002
Tl	205	4.0×10^8	0.0002
Pb	208	3.7×10^8	0.0007
Bi	209	3.4×10^8	0.0005
U	238	2.3×10^8	0.0001

48. As described in the '386 and '698 Patents, the use of isotopes, and specifically isotopes of lanthanides and/or noble metals, can expand the multiplexing options for labelling with the elemental tags (*see, e.g.*, '386 Patent, 5:52-57; 8:17-25 "a large number of distinguishable element and isotopes can be used as tags"; 9: 24-36; 9:56-57 "the tags can be conveniently constructed using the natural isotopic distributions"; 9:67-10:9 of '386 "Where a higher order of multiplexing is desired, the use of commercially-available enriched isotopes .. offers a possibility"). For example, referring to the example above with the first elemental tag comprising Europium and the second elemental tag comprising Gadolinium, multiplexing with these elements can be expanded by selecting the first elemental tag comprising Europium to be a specific Europium isotope (e.g. ^{151}Eu), such that a third elemental tag also comprising

Europium, but of a different isotope thereof (e.g. ^{153}Eu) could be provided, giving three elemental tags total (^{151}Eu, ^{153}Eu and Gd) that can be used for multiplexing and providing distinguishable signals to identify multiple different analytes in a sample.

Single Cell Analysis

49. The '386 and '698 Patents further provide methods for single cell analysis, or in other words, analysis at the individual cellular level (versus the multi-cellular level), using the multiplexing and mass spectrometry methods above (*see, e.g.* '386: 1: 35-37 "The invention features apparatus and methods for sequentially analyzing particles, for example single cells or single beads, by spectrometry"). That is, the methods and systems described therein are capable of identifying analytes and/or biomarkers that are present in or on a specific individual cell. This level of specificity in detection provides a powerful tool for analysis and diagnosis on the individual cell level, such as for example in identifying different biomarkers present in different cells in a cell sample (e.g. different cells in a tissue sample), and in differentiating between different cells in a sample (e.g. cancerous cells versus non-cancerous cells) based on their individual biomarker profiles. As described in the '386 and '698 Patents themselves, some examples where single cell analysis was believed to be beneficial at the 2004 time of filing were in the subclassification of non-Hodgkin's lymphoma, immunotyping of helper T-cells, and the determination of the ratio of CD4 to CD8 T-cells for the indication of HIV progression in HIV positive patients (*see, e.g.*, '386: 1:66-2:4). In the years since the filing of the '386 and '698 Patents, the ability to perform analysis on the single cell level has allowed for advances in the fields of, for example cancer

research and immuno-oncology, immunology, immunophenotyping, infectious disease/microbiology studies (including studies on COVID-19), liquid biopsy, neurology, oncology, and stem cell research (*see* discussion above).

50. As a part of the single cell analysis described in the '386 and '698 Patents, a transient signal of multiple vaporized, atomized, and ionized elemental tags of a first cell is detected using mass spectrometry, and a transient signal of multiple vaporized, atomized, and ionized elemental tags of a second cell are detected using mass spectrometry, with the transient signal associated with the first cell and the transient signal of the second cell being detected sequentially. The elemental composition (in '386) or the lanthanides and/or noble metals (in '698) of the first and second cells are thus detected via this multiplexing single cell analysis technique. That is, the '386 and '698 Patents provide systems and methods that allow for the sequential detection of the transient signals of the multiple vaporized, atomized and ionized elemental tags, with the transient signals each being associated with either the first or second cell in such sequential detection, and by so doing provide for the multiplexed analysis of analyte at the individual cell level.

PERSONS OF ORDINARY SKILL IN THE ART

51. For the purpose of my analysis and opinions, I have considered how certain terms and limitations in the ‘386 and ‘698 Patents would been understood at the time of applications for the inventions claimed in each respective patent by a person of ordinary skill in the art.

52. The ‘386 and ‘698 Patents reflect that they are based upon and claim priority to a Provisional Application, Serial No. 60/555,952, that was filed on March 25, 2004.

53. In determining the characteristics of a person of ordinary skill in the art at the time of the respective applications (March 25, 2004 for the ‘386 and ‘698 Patents), I considered several things including, for example, the type of technology involved, the educational background and experience of those actively working in the field at the time, the backgrounds and experience of the scientists and engineers that I worked with in the mass spectrometry field at about that time, and the types of problems encountered.

54. In my opinion, a person of ordinary skill in the art as of March 25, 2004 would be a person who has: (i) a graduate degree, and preferably a Ph.D., in a relevant scientific or engineering field (such as materials science, chemistry, physics, materials engineering, medicine, and/or biophysics); and/or (ii) approximately ten (10) years of relevant industry or academic experience relating to mass spectrometry techniques and/or applications thereof.

LEGAL STANDARDS

55. I understand that, generally, terms in a claim are generally given their plain and ordinary meaning as would have been understood by one of skill in the art at the time that the application for the patent at issue was made. I also understand that a patentee may act as his own lexicographer and expressly or implicitly define a term or terms in

a manner that differs from their plain and ordinary meaning. For this reason, I understand that when I interpret a claim term of a patent, my primary source is the intrinsic evidence of the patent which is comprised of the claims, the specification, and the prosecution history. Further, it is my understanding that in interpreting the meaning of claim terms and limitations, you first look to how a term or limitation is used in the claims, and then how the term or limitation is used in the context of the entire patent, including the specification. I understand that statements and arguments made by the inventors during the prosecution of their patent application (also called the "file history") may also be considered in determining the meaning and scope of a claim. I understand that one may also look to extrinsic evidence such as technical dictionaries, treatises and even my own knowledge as one of skill in the art. I understand that extrinsic evidence may not be used to contradict the intrinsic evidence as to the meaning of a claim term or limitation (*Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (*en banc*)).

CLAIM CONSTRUCTION

56. I have reviewed the claim terms and limitations in dispute, reviewed and assessed the intrinsic evidence, and formulated opinions as to what the terms and limitations would mean to a person of ordinary skill in the art at the time of the respective applications. The following reflects my opinions regarding the proper constructions of the identified disputed claim terms and limitations.

A. "Vaporizing, Atomizing and Ionizing" ('386 and '689 Patents)

Claim Term(s)	Fluidigm's Proposed Construction
"vaporizing, atomizing and ionizing" '398/'698 Patents	Generating ionized atomic components from a solid or liquid state of a sample
"vaporizing, atomizing and ionizing multiple elemental tags" '386 Patent	Generating ionized atomic components of multiple elemental tags from a solid or liquid state of a sample
"vaporize, atomize and ionize multiple elemental tags" '698 Patent	

57. I understand that dependent Claims 6, 9-10 and 18-19 of the '386 Patent, and Claims 5 and 6 of the '698 Patent, are involved in the subject lawsuit ("'386/'698 Asserted Claims"), that these claims each depend from an independent Claim 1, and the corresponding Claim 1 recites the term "vaporizing, atomizing and ionizing" ('386 Patent) or "vaporize, atomize, and ionize" ('698 Patent).

58. In my opinion, a person of ordinary skill in the art at the time of the filing of the application which resulted in the '386 and '698 Patents, including myself, would understand that the term "vaporizing, atomizing and ionizing," as used in the subject

claims, specification, and file history, means "*generating ionized atomic components from a solid or liquid state of a sample*."

59. The '386 and '698 Patents are directed to mass spectrometry based multi-parametric particle analysis ('386 and '698 Titles and Abstracts) (while certain relevant representative citations to the '386 Patent are referred to in this Report, the corresponding sections of the '698 Patent are likewise identified as the '386 and '698 Patents and share the same specification[3]). Specifically, for example, both the '386 and '698 Patents explain that "[t]he elemental composition of the particle or elemental tag is determined by a spectrometer 106 operatively connected to the device 104. Spectrometer 106 may, for example, include a mass spectrometer 106 which detects the ions" ('386 Patent, 7:56-61). Both independent Claims 1 of the respective '386 and '698 Patents also require that detection is performed by mass spectrometry ("... detecting, using mass spectrometry..." Claim 1 of '386 Patent; "... detect, by mass spectrometry ..." Claim 1 of '698 Patent).

60. A person of ordinary skill in the art at the time, including myself, understood that in order to perform mass spectrometry techniques, the ability to generate ions from a solid or liquid material, including vaporized, atomized, and ionized elemental tags as described in the patents, was critical. This is because, as discussed in the Background section above, mass spectrometry techniques require the presence of ions for analysis

[3] The '386 and '698 Patents both claim priority to the same underlying non-provisional Patent Application Serial No. 11/089,02 filed on March 25, 2005, which in turn claims priority to the same underlying provisional Patent Application Serial No. 60/555/952. Accordingly, while certain cross-reference information may be different, the specification of the '386 Patent is otherwise identical to that of the '698 Patent, and so the '386 specification is referred to herein.

(*see, e.g.*, "mass/charge detection channels" '386 Patent, 8:21-22; Rubakhin Section 2.2.1 Ion Sources "analytes ... need to be ionized"; Blades page 13A).

61. Specifically, the mass spectrometry techniques described in the '386 and '698 Patents are capable of distinguishing between different ions on the basis of their differing mass-to-charge ratios. Since the ionized atoms generated by vaporizing, atomizing, and ionizing the elemental tags in '386 and '698 will, for the most part, have the same charge, the different masses of the ions can be used for the purposes of distinguishing them. Because neutral atoms do not have a charge, mass spectrometry techniques generally would not be useful for differentiating between them (although there are certain special cases, not relevant here, where neutrals gain kinetic energy and may be detected). As a result, generating the ionic form of the material to be analyzed is critical to successfully carry out the claimed mass spectrometry technique.

62. The '386 and '698 Patents teach that elemental tags are broken down, "vaporized, atomized and ionized," into their ionized atomic components to allow for detection and mass-differentiation between element tags used to tag different analytes in or on cells of interest (*e.g.* "a spectrometer to analyze the vaporized, atomized and ionized . . . elemental tag associated with the particles"; "means to vaporize, atomize and ionize the particles and/or any tags that may be associated with the particles"). ('386 Patent, 3:56-58, 6:51-52). That is, the patents teach that the chemical moiety being detected and/or distinguished is the ionized atomic components of the lanthanide and/or noble metal of the element tag itself (*e.g.* the ionized lanthanide and/or noble metal (including isotopes thereof), as obtained by breaking down the elemental tag to the lanthanide and/or noble metal atomic component) (*see, e.g.,* '386 Patent, 7:56-60

"The elemental composition of the ... elemental tag is determined"). The elemental tags are vaporized because they are liberated from the solid or liquid state of the sample. The elemental tags are atomized because the free atoms are separated from the biomolecules to which they were attached. And the elemental tags are ionized because they are charged. There is no specific method or limitation on the method by which the elemental tags are "vaporized, atomized, and ionized" so long as ionized atomic components are generated from a solid or liquid state of a sample.

63. This fact is further supported by descriptions in the '386 and '698 Patents that "the amount of tag element detected by the mass spectrometer is proportional to the amount of tagged affinity product bound to the cell" ('386 Patent, 10: 28-30) and "the method offers the potential for massively multiplexed assay ... with essentially no signal overlap [such as] [w]here the elemental (isotopic) tags are quantitatively associated with specific affinity products" ('386 Patent, 10: 43-49). The '386 and '698 Patents describe the ability to distinguish between the masses of ionized lanthanides and/or noble metals (and isotopes thereof) used as the elemental tags to facilitate multiplexing and allows for simultaneous detection of multiple different analytes in the cells being analyzed.

64. As described above, there were a variety of techniques available to persons of ordinary skill in the art in 2004 to generate ionized atomic components from a sample suitable for detection with mass spectrometry. A common feature of all such techniques was to impart energy to a sample to liberate the moieties of interest in an ionized form from a solid or liquid phase (*see, e.g.*, Rubakhin Section 2.2.1 Ion Sources "analytes need to be vaporized from a solid or liquid phase, ionized and

transferred into the vacuum system of the mass analyzer"). The mechanisms by which energy could be imparted to the sample included, for example, heating of the sample, exposure of the sample to a high electric field, applying laser irradiation, bombardment with ions, and other methods (*see, e.g.*, Rubakhin page 3; "[v]aporization can be achieved by a variety of techniques, including heating the samples, exposing them to a high electric field ... and/or via bombardment with fast atoms, or atomic or molecular ions").

65. The '386 and '698 Patents identify several exemplary representative devices suitable to impart energy to "vaporize, atomize, and ionize" elemental tags. For example, both patents disclose an open-ended list of several suitable devices, all which have the common feature of imparting energy to "vaporize, atomize, and ionize" the targeted tags: "[t]he means to vaporize, atomize and ionize the single particles may include glow discharge, graphite furnace, and capacitively coupled plasma devices, or other suitable devices" ('386 Patent, 6:59-63). The inventors clearly did not intend for this list to be exclusive, rather the inventors expressly used the phrase "or other suitable devices." *Id.* Indeed, the inventors went even further by stating that "[a]ny means 104 suitable for the purposed disclosed herein can be employed to vaporize, atomize and excite or ionize the particle or the elemental tag associated with the particle . . ." ('386 Patent, 13:2-5). While the patents describe several specific preferred embodiments, the disclosures are clear that the invention is not limited to those embodiments.

66. In 2004, there were a variety of methods and devices to impart energy to vaporize, atomize, and ionize elemental tags beyond the ICP and glow discharge techniques identified in the application (*see, also,* Col. 13, Lines 1-12 and Col. 13,

lines 12-39 of '386; page 14A of Blades for ICP, and Col 13, lines 1-12 of '386; Blades page 16A, Bogaerts page 669, for glow discharge), such as for example, microwave induced plasma, spark source, laser ablation/ionization, and electrospray techniques (*see* page 13A of Blades), and secondary ion mass spectrometry (SIMS) techniques (*see*, e.g., Colliver, page 2225; Blades, page 16A). Accordingly, in my opinion, a person of ordinary skill would have understood from the specifications that the patents teach that a variety of different instruments and techniques may be used to generate ionized atomic components of the elemental tags per the vaporization, atomization and ionization process recited in the claims.

67. Additionally, that the '386 and '698 Patents both specifically describe glow discharge as a suitable technique for vaporization, atomization and ionization, would in my opinion also indicate to a person of ordinary skill in the art that SIMS techniques were also encompassed by the invention, since SIMS instruments also operate by a "sputtering" mechanism like glow discharge devices. As discussed above, both glow discharge and SIMS techniques share a "sputtering" mechanism for the formation of ionized material, in which "primary ions" (from a discharge plasma in glow discharge techniques, or from an ion gun in SIMS techniques) are accelerated towards a sample to be analyzed, with the kinetic energy of the ions being transferred to the sample on impact, and thereby causing surface material to be ejected from the sample surface - - the "sputtering" phenomenon. (For glow discharge, *see, e.g.,* Bogaerts, page 669, "[t]he use of glow discharge as an ion source for mass spectrometry is based on the phenomenon of sputtering": Blades, page 16A, "[t]he impinging ion ... penetrates to a depth of a few angstroms where its kinetic energy can cause surface atoms to be

ejected ... a phenomenon called sputtering". For SIMS *see, e.g.*, Blades page 16A; Rubakhin, Section 2.2.1.1, "The bombardment process results in formation of gas phase neutrals, ions ...").

68. In both the glow discharge and SIMS techniques, sample material liberated from the sample is ionized, and these "secondary ions" are provided to a mass analyzer/detector for analysis. The SIMS process that operates by sputtering is a vaporization, atomization and ionization technique, just as in the glow discharge technique (*See, e.g.*, Blades page 16A; Rubakhin, Section 2.2.1.1, "The bombardment process results in formation of gas phase neutrals, ions ..."; "Methods for Generating Protein Molecular Ions in TOF-SIMS" by McArthur et al., Langmuir 2004, 20, 3704-3709 (hereinafter referred to as "McArthur"), Abstract, "The vaporization process used in TOF-SIMS ..."; "Atomic and Molecular Imaging at the Single-Cell Level with TOF-SIMS" by Colliver et al., Anal. Chem 1997, 69, 2225-2231 (hereinafter referred to as "Colliver"), page 2225 "SIMS can now be used to investigate ... important biological molecules ... [that] desorb directly into the gas phase using energetic ion beams.")

69. Further, the fact that the '386 and '698 Patents describe employing TOF MS expressly teaches and discloses to those skilled in the art that the inventions encompass pulsed types of ion generating devices such as SIMS and laser ablation. In 2004, people of ordinary skill in the art understood that creating ions for SIMS and laser ablation provided the level of precision necessary to determine when an ion left a sample to accurately achieve and measure TOF. (*See, e.g.* '386 Patent, Abstract; 1:18-20; Claim 17; Claim 19).

70. I reviewed IONpath's proposed construction of the term "vaporization, atomization and ionization" and "vaporize, atomize and ionize" (including with and without the additional words "multiple elemental tags"), which IONpath proposes means: *"to convert the elemental tags to a gas by heating, separate the resulting gas into atomic constituents, and positively or negatively charge those atomic constituents.* In my opinion, IONpath's proposed construction is incorrect and ambiguous.

71. As an initial point, I note that IONPath's proposed construction seems, in essence, to agree with Fluidigm's proposed construction, in that IONpath's construction also results in "positively or negatively charged atomic constituents" (akin to "ionized atomic components" in Fluidigm's construction). However, in my opinion, where IONPath errs is in adding further unnecessary limitations to this base construction that are extraneous and not supported by the '386 and '698 specification, claims, and file history.

72. First, IONpath's proposed definition adds a limitation – *heating* – which is not present in any of the claims, is not explicitly or implicitly required by any of the claims, and, in my opinion, is not a limitation encompassed within or otherwise required to "vaporize, atomize, and ionize" elemental tags. When a material is vaporized at the atomic scale (such as in glow discharge or SIMS techniques) and the liberated atoms are ionized, the process is correctly governed by quantum mechanics. Classical treatments of such processes fail. The proposed addition of the limitation "heating" is not and would not, in my opinion, be understood to persons of ordinary skill in the art at the time to be required within the term "vaporization, atomization, and ionization" including as used in the subject claims and patents. These are quantum

mechanical processes. In the limit of very large numbers, classical theory may be used to describe the behavior of a collective of quantum mechanical objects. The term "heating" and "heat" refer to interactions between atoms or molecules in large *collectives* such as atoms in a solid, liquid, or gas. When referring to single atoms or molecules or small numbers of atoms or molecules, these terms do not clearly apply. If an energetic atom or ion transfers energy to a less energetic atom or ion, one would not refer to this as "heating" of the atom or ion. Thus, the term "heat" is reserved for the very specific concept of the transfer of thermal energy between two "systems" where "systems" refers to macroscopic collections of atoms.

73. Second, the proposed addition of the limitation "heating" is also not meaningful in the context of "vaporizing, atomizing, and ionizing" elemental tags in mass spectrometry. As people of ordinary skill in the art understood, there are many ways to vaporize, atomize, and ionize particles and *all* devices used to vaporize, atomize, and ionize particles or elemental tags must employ energy to liberate ionized atomic components. This is true for ICP, capacitively coupled plasma, a graphite furnace, glow discharge, and SIMS – all such devices use energy to liberate ionized atomic components. For example, "vaporization" of a sample can be achieved by a variety of different processes including heating of the sample, exposure of the sample to a high electric field, applying laser irradiation, bombardment with ions, and other methods that are capable of imparting energy to the sample to liberate the material to be detected from the sample (*see, e.g.*, Rubakhin page 3; "[v]aporization can be achieved by a variety of techniques, including heating the samples, exposing them to a high electric field ... and/or via bombardment with fast atoms, or atomic or molecular ions").

In other words, in my opinion, there is no reason to believe that "heat" is necessary for vaporization, atomization and ionization of elemental tags in a sample. Another example of a technique where ionization can be achieved without heat is in the field evaporation of ions. In this technique, a specimen of tungsten, a high-melting-temperature metal, can be vaporized, atomized, and ionized at 4K solely by application of a high electric field. There is no “heat” involved in this process (*see, e.g.*, page 55-58 of "Local Electrode Probe Tomography: A User's Guide" by Larson et al. (and including myself as co-author), Springer, 2013).

74. I understand that IONpath is relying upon, or may rely upon, the ‘386 and ‘698 Patents reference to a preferred embodiment that employs ICP and explains that, with that device, a sample is injected into a high temperature plasma. (‘386 Patent, 12:34; 13: 31-32; Joint Claim Construction & Prehearing Statement, Exhibit 1, p.2). The ‘386 and ‘698 Patents, as previously stated, do not limit the method to “vaporize, atomize and ionize” to any specific device and, indeed, identify and permit numerous devices and expressly state that “any means suitable” “to vaporize, atomize and excite or ionize” may be used. (‘386 Patent, 13:2-5). Further, none of the *claims* in either the ‘386 Patent or ‘698 Patent use the word or term “heat” or limit the manner to “vaporize, atomize and ionize” multiple elemental tags by using “heat.” Nor, in my opinion, would a person of ordinary skill in the art at the time understand the claims to limit the device used to “vaporize, atomize and ionize” to requiring the use of “heat.” Again, the ‘386 and ‘698 Patents teach “vaporizing, atomizing and ionizing” elemental tags by using devices that employ an exchange of energy which may be a single quantum of energy or a very large number of quanta of energy that is exchanged.

75. While a preferred embodiment in the patents describes the use of ICP, heat transfer, and a high temperature plasma, this is simply one description of one manner to apply energy to a sample. In my opinion, had the inventors intended to limit the claims to ICP, or the use of a certain type and specific temperature of plasma, they would have done so. However, no such limitations appear in the claims, the specifications broadly describe the use of "any means" to achieve vaporization, atomization and ionization, and, in my opinion, persons of ordinary skill in the art at the time would not understand "vaporization, atomization and ionization" as used in the claims to be limited to the application of "heat," nor would one conclude that the patents do not encompass SIMS.

76. It is also worth mentioning what is meant by "heat transfer" and "high temperature plasma" in the context of ICP. As was understood by persons of ordinary skill in the art at the time of the applications, ICP plasma contains argon atoms that have been excited via application of an inductively coupled electric field to ionize the argon atoms and form a plasma containing highly energetic argon ions and free electrons (*see, e.g.,* '386 13: 21-30). The temperature of plasma, as would be understood by those of ordinary skill in the art, is a function of the average kinetic energies of these highly energetic argon ion and electron species. As understood on the atomic level, the transfer of energy from the plasma to the sample actually occurs via impact of these energetic species with the sample introduced into the plasma (*see, e.g.,* Thomas 2001-2002, pages 29-30 of Part III "The final process of conversion of an atom to an ion is achieved mainly be collisions of energetic argon electrons (and to a lesser extent argon ions)"). In other words, the "heat" can be understood as a measure

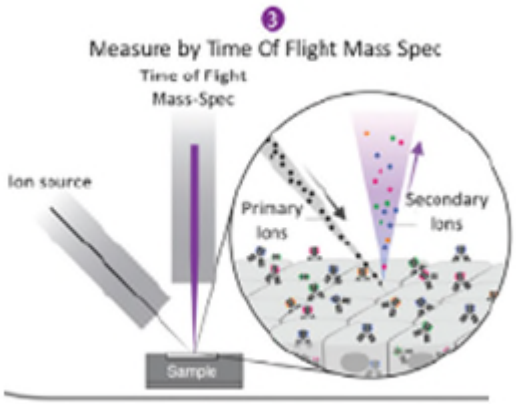
of the average kinetic energy of excited ion species, but it is this kinetic energy itself -- impact of the energized plasma species with the sample -- that causes the vaporization, atomization and ionization of particular elements within the sample.

77. Similarly, in the glow discharge method explicitly described in the '386 and '698 Patents as being a suitable technique for vaporization, atomization and ionization (*see, e.g.*, "386 Patent 6:59- 7:2), the liberation of atoms from a sample surface, and generation of ions, occurs via transfer of kinetic energy from ionized plasma species to a sample -- causing "sputtering" of the sample (*see, e.g.*, Blades, page 16A; Bogaerts 669). That is, the glow discharge technique does not use *heat* to liberate material from a sample, but instead operates by this "sputtering" mechanism. The fact that the inventors of the '386 and '698 Patents used the vaporization, atomization, and ionization language to describe the “sputtering” process of the glow discharge method is further consistent with my understanding that vaporization, atomization, and ionization can also occur via transfer of kinetic energy from energetic ionized species (e.g. bombardment by primary ions) to a sample, as opposed to requiring "heat" per se.

78. In SIMS as well, the transfer of kinetic energy from a beam of fast-moving ions (or, indeed, a single fast-moving ion) directed onto a sample causes the vaporization, atomization and ionization (*see* Rubakhin Section 2.2.1 Ion Sources "vaporization can be achieved ... via bombardment with fast atoms, or atomic or molecular ions," and Section 2.2.1.1 "The bombardment process results in formation of gas phase neutrals, ions .."; McArthur Abstract and Introduction; Colliver page 2225). One of ordinary skill in the art would understand that it is the transfer of energy from excited species, i.e. from the energized ions and/or plasma species, that is critical to the formation of

the ionized atomic components for mass spectrometry analysis, and that the transfer of energy may be achieved by numerous methods available and as taught at the time of the '386 and '698 Patents other than ICP.

79. Indeed, as discussed above, those of ordinary skill in the art have consistently used the term “vaporization” to refer to the SIMS process. (*See, e.g.*, Blades page 16A; Rubakhin, Section 2.2.1.1, "The bombardment process results in formation of gas phase neutrals, ions ..."; "Methods for Generating Protein Molecular Ions in TOF-SIMS" by McArthur et al., Langmuir 2004, 20, 3704-3709 (hereinafter referred to as "McArthur"), Abstract, "The vaporization process used in TOF-SIMS ..."; "Atomic and Molecular Imaging at the Single-Cell Level with TOF-SIMS" by Colliver et al., Anal. Chem 1997, 69, 2225-2231 (hereinafter referred to as "Colliver"), page 2225 "SIMS can now be used to investigate ... important biological molecules ... [that] desorb directly into the gas phase using energetic ion beams.") (*See, also*, Keren, page 1374, below for an image of SIMS vaporization in the MIBIscope):



80. To construe “vaporization, atomization, and ionization” in a manner to exclude SIMS would be fundamentally inconsistent with the understanding of those of ordinary skill in the art as evidenced by these many references.

81. In my opinion, one of ordinary skill in the art at the time of the application for the '386 and '698 Patents would not understand the phrase "vaporization, atomization or ionization" to require “heat,” much less to be limited to ICP. Rather, a person of ordinary skill in the art at the time would plainly understand the term to include any technique or device, including ICP, glow discharge, and SIMS, where ionized atomic components are generated from the transfer of energy to a sample.

82. My review of the prosecution history for the '386 and '698 Patents is consistent with my opinion. Nothing within the prosecution histories, in my opinion, reflects that “vaporization, atomization, and ionization” is somehow limited by the term “heat” or that the limitation requires the term “heat.” For example, I understand that no amendments were made to the phrase "vaporization, atomization, ionization" during prosecution of the '386 and '698 Patents to overcome any cited references or to otherwise address any deficiency in the claim. Also, I understand that no arguments were necessary or were made in the prosecution of the '386 and '698 Patents to distinguish "vaporization, atomization and ionization" from any prior references. Accordingly, the prosecution history supports the plain language in the specification that any means suitable to vaporize, atomize and ionize may be used.

83. If IONpath’s argument is that the “vaporize, atomize and ionize” cannot be achieved using a SIMS device based upon its contention that the claim limitation

requires “heat,” I disagree. Persons of ordinary skill in the art at the time understood that SIMS processes necessarily involve the transfer of *some* heat, by basic thermodynamic principles (impinging ions on a surface of a sample will cause a change in temperature and heat of the sample), just as in glow discharge and other techniques. In SIMS, the primary ion may have 1000 times the amount of energy needed to liberate a secondary ion. The remainder of the energy ultimately ends up in atomic vibrations of the specimen (referred to as phonons). One might correctly state that this excess energy ended up as “heat” in the sample because atomic vibrations of this type are a collective phenomenon and would affect the sample. The individual secondary ion, however, is not “heated” in this process.

84. Additionally, IONpath's proposed construction that the term “vaporization, atomization, and ionization” requires conversion to a gas by heating is flawed in that it seeks to import an entirely new limitation and requirement that is completely absent from the claims and tries to impose the alleged feature of one (of many) devices into the claims. There is no point in either the claims or the specifications of the '386 and '698 Patents where “heat” is required for vaporization, atomization, and ionization.

85. I believe it is possible that IONpath has arrived at its proposed definition by equating the word "vaporization" with an overly rigid definition of the word "gas" that does not apply to the technique here, even though one of ordinary skill in the art would understand that the formation of a "true" gas, strictly speaking (i.e. having a sufficient numbers of atoms or molecules such it exerts a pressure, etc., approaching that of the ideal gas law PV=nRT), is not required for the generation of the ionized atomic components. Indeed, the classical use of the term “gas” in describing a collection of

atoms and molecules is similar to the use of the term “heat” to describe the energy in a collection of atoms and molecules. The properties of a gas, similar to “heat,” are an average over a large number of atoms and molecules. Any single atom or molecule can have an energy which is much higher or lower than the average. Classical descriptions of these phenomena such as “gas” and “heat” do not apply to small numbers of atoms and molecules. Here, whether or not a "true" gas is formed, one of ordinary skill in the art would understand that what is critical to the technique is that the elemental tags in the cells are broken down to liberate the ionized atomic components thereof (i.e. whether this liberated state is a "true" gas or not is immaterial), for example the sample with elemental tags is subjected to a technique that transfers energy to break bonds, disrupt cellular material, and ultimately atomize and ionize the elemental tags to allow for mass-differentiation between different tags.

86. In the event IONpath’s proposed construction intends to assert that “vaporization, atomization and ionization” as used in the claims requires a series of specific, sequential, steps (*e.g.* convert to a gas by heating, then separating the gas into constituent components, and then positively or negatively charging the atomic constituents), I disagree. There is no such limitation or requirement in “vaporization, atomization, and ionization” in the claims, or in the specification. Indeed, both patents disclose that the vaporization, atomization and ionization can occur in the same or different devices, thus at the same time or different times (*see, e.g.*, '386 13: 7-9:"[i]n some instances, vaporization, atomization and ionization ... can occur in different devices and at different times"). In other words, the patents teach, and a person of ordinary skill would understand, that ionization can occur simultaneously or directly

after vaporization, the key being that ionized atomic components are generated. As yet another example of a technique in which simultaneous ionization and vaporization occur, in field evaporation, atoms or molecules on the specimen surface are vaporized and ionized in the same step. The electric field causes an atom or molecule on the surface to lose an electron and become ionized and then it is accelerated away into the vapor by the electric field. Thus, vaporization and ionization occur simultaneously (*see, e.g.*, pages 55-58 of Local Electrode Prove Tomography: A User's Guide" by Larson et al. (and including myself as co-author), Springer, 2013).

87. In my opinion, a person of ordinary skill in the art at the time would not understand the term “vaporization, atomization and ionization” to mean or require a sequence or order, but instead would understand that a simultaneous occurrence, or any sequence, that results in the generation of ionized atomic components is taught and claimed. Notably, with respect to the glow discharge technique described above, at least the vaporization and atomization of material occurs simultaneously with bombardment by plasma ions (*see*, Bogaerts, page 669, "The sputtered atoms arrive in the plasma where they can be ionized"), further evidencing that the '386 and '698 Patents contemplated techniques where parts of the vaporization, atomization and ionization process occurred simultaneously, and not as separate and specific sequential steps.

88. Accordingly, it is my opinion that the term “vaporization, atomization and ionization” as used in the claims of the ‘386 and ‘698 Patents means “generating ionized atomic components from a solid or liquid state of a sample” or, when the

phrase is followed by the language “multiple elemental tags,” then “generating ionized atomic components of multiple elemental tags from a solid or liquid state of a sample.”

B. “First Device” / "Second Device ('698 Patent)

Claim Term(s)	Fluidigm's Proposed Construction
“A first device to vaporize, atomize and ionize multiple elemental tags from a single first cell of the plurality of tagged cells and multiple elemental tags from a single second cell of the plurality of tagged cells" '698 Patent	• "a first device": Plain and ordinary meaning. • "vaporize, atomize and ionize": Generate ionized atomic components from a solid or liquid state of a sample.
"A second device to detect, by mass spectrometry, lanthanides and/or noble metals of the single first cell by detecting a transient signal of the multiple vaporized, atomized and ionized elemental tags of the first cell, and lanthanides	• "a second device": Plain and ordinary meaning. • "lanthanides": Any element having atomic numbers 57-71 • "noble metals": Any of several metallic elements, the electrochemical potential of which is much more positive than the potential of the standard hydrogen electrode, therefore, an element that resists oxidation. Examples include palladium, silver, iridium, platinum and gold. • "transient signal": The detectable ions generated for a

and/or noble metals of the second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single second cell, wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially" '698 Patent	limited duration of time. • "vaporizing, atomizing and ionizing": Generating ionized atomic components from a solid or liquid state of a sample. • "detected sequentially": Observed at separate times.

89. I understand that Fluidigm is asserting Claims 5 and 6 of the ‘698 Patent in the lawsuit (the “’698 Asserted Claims”). Both ‘698 Asserted Claims depend from independent Claim 1 of the ‘698 Patent which contains the terms “first device” and “second device.”.

90. In my opinion, a person of ordinary skill in the art at the time of the filing of the application for the '698 Patent would have understood that the terms “first device” and “second device” as used in the ‘698 Patent, including Claims 1, 5 and 6, are used in a common and ordinary manner to refer to the types of devices claimed and taught by the

patent to vaporize, atomize, and ionize multiple elemental tags (first device) and detect, by mass spectrometry, lanthanides and/or noble metals (second device).

91. A person of ordinary skill in the art would understand from the ‘698 Patent the types of common devices that may be used as the "first device" and "second device" as set out in the claims. For example, with respect to the "first device," a person of ordinary skill in the art would understand what device may be used as the "first device to vaporize, atomize, and ionize multiple elemental tags." The specification of the ‘698 Patent supports this and explains that "[a]ny means suitable for the purposes disclosed herein can be employed to vaporize, atomize and excite or ionize the particle or the elemental tag associated with the particle, for example, graphite furnace, glow discharge and capacitively coupled plasma" (‘698 Patent, 13:2-6), "an inductively coupled plasma (ICP) device" ('698 Patent, 6:63-64), as well as "other suitable devices" ('698 Patent, 6:59-63). A person of ordinary skill in the art would understand from the claims and specification of the ‘698 Patent that its disclosure that "other suitable devices" ('698 6:63) are acceptable necessarily includes other commonly known devices to "vaporize, atomize and ionize" including, for example, microwave induced plasma, DC-glow discharge, RF-glow discharge, spark source, laser ablation/ionization, ion-beam (including, but not limited to, SIMS), electrospray, capacitive microwave plasma, and direct current plasma.

92. Additionally, the fact that the ‘698 Patents describe employing TOF MS expressly teaches and discloses to those skilled in the art that the claimed device also encompasses pulsed types of ion generating devices such as SIMS and laser ablation. In 2004, people of ordinary skill in the art understood that creating ions employing

SIMS and laser ablation provided the level of timing precision necessary to determine when an ion left a sample to accurately achieve and measure ToF. (*See, e.g.* '386 Patent, Abstract; 1:18-20; Claim 17; Claim 19).

93. With respect to the claimed "second device," a person of ordinary skill in the art at the time would understand from the claim alone that the device is a common and ordinary instrument used by scientists at the time, a mass spectrometer, to detect transient signals. Persons of skill in the art at that time regularly employed common mass spectrometry technology to detect transient signals. This understanding is further supported by the specification of the '698 Patent, which discloses common, ordinary, and exemplary mass spectrometry instrumentation that may be implemented as the second device, including ToF MS, simultaneous or sequential mass analyzers, array-detector magnetic sector, 3D ion trap, linear ion trap, quadrupole devices, equivalents thereof (*see e.g.*, '698 17:66-18:3 and 18:6-23), and also describes forms of ion pretreatment and other instrumentation that can be implemented as a part of the second device (*see, e.g.*, '698 14:6-19:43).

94. It is my understanding that IONpath contends that the language "*a first device to vaporize, atomize, and ionize multiple elemental tags from a single first cell of the plurality of tagged cells and multiple elemental tags from a single second cell of the plurality of tagged cells*", as well as "*a second device to detect, by mass spectrometry, lanthanides and/or noble metals of the single first cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single first cell, and lanthanides and/or noble metals of the single second cell by detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single*

second cell, wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially" are governed by 35 U.S.C. § 112(6). Further, it is my understanding that IONpath contends that the claimed "first device" is limited to:

> "a glow discharge, graphite furnace, capacitively coupled plasma device, or inductively coupled plasma device, with an input configuration to receive the output of a cell or particle injector systems in use for flow cytometry, including sheath flow injection systems, and equivalents thereof."

And, that the claimed "second device" is limited to:

> "a quadrupole, magnetic sector with array detector, 3D Ion Trap or Linear Ion Trap mass spectrometer, a time of flight mass spectrometer, and equivalents thereof."

95. I am not a patent attorney, or an expert in patent law, and provide no opinion regarding as to whether 35 U.S.C. § 112(6) should be applied to the "first device" and the "second device." However, if IONpath's proposed language were adopted by the Court, I do have opinions regarding what instruments are disclosed by the '698 Patent, as well as what instruments comprise equivalents of such types of equipment.

96. For example, with respect to the "first device," the '698 Patent explains that "[a]ny means suitable for the purposes disclosed herein can be employed to vaporize, atomize and excite or ionize the particle or the elemental tag associated with the particle, for example, graphite furnace, glow discharge and capacitively coupled plasma" ('698 Patent, 13:2-6), "an inductively coupled plasma (ICP) device" ('698 Patent, 6:63-64), as well as "other suitable devices" ('698 Patent, 6:59-63). A person of

ordinary skill in the art would understand from the ‘698 Patent that its disclosure that "other suitable devices" ('698 6:63) are acceptable necessarily includes other commonly known and equivalent devices to "vaporize, atomize and ionize" including, for example, microwave induced plasma, DC-glow discharge, RF-glow discharge, spark source, laser ablation/ionization, ion-beam (including, but not limited to, SIMS), electrospray, capacitive microwave plasma, and direct current plasma.

97. Additionally, the fact that the ‘698 Patent describes employing ToF MS expressly teaches and discloses to those skilled in the art that the claimed “first device” encompasses pulsed types of ion generating devices such as SIMS and laser ablation. In 2004, people of ordinary skill in the art understood that creating ions employing SIMS and laser ablation provided the level of precision necessary to determine when an ion left a sample to accurately achieve and measure ToF. (*See*, *e.g.* ‘386 Patent Abstract; 1:18-20; Claim 17; Claim 19).

98. Also, in my opinion, I believe that IONpath's proposed construction to require "an input configuration to receive the output of a cell or particle injector systems in use for flow cytometry, including sheath flow injection systems, and equivalents thereof,” as a part of the "first device" is wrong. Nowhere do the '386 and '698 Patents require that such a cell or particle injector system be a part of a device to vaporize, atomize, and ionize multiple elemental tags. Instead, the '386 and '698 Patents are clear that any equipment upstream of the claimed “first device to vaporize, atomize, and ionize,” including “sample introduction systems,” are *separate* devices. (‘698 Patent: 11:50-53, “The sample introduction system 102 can comprise several devices that are currently in use with other flow cytometry sample introduction systems”; 11:63-67 “All sample

introduction devices suitable for the purposes disclosed herein; including ICP devices, will serve, regardless of whether they now exist or are hereafter developed or improved."; 6:8-12, "particles that have been introduced into a device to vaporize, atomize and excite or ionize them"). In my opinion, a person of ordinary skill in the art would understand that the claimed "first device to vaporize, atomize, and ionize" does not include equipment (entirely different "devices") used to feed samples into the "first device to vaporize, atomize, and ionize." Nor can a specific input configuration be required for the "first device to vaporize, atomize, and ionize," as the Patent makes clear that the "first device" does not include or encompass a "sample introduction system" and, further, the specification explains that several exemplary different devices were available that could be used at the time, and that the invention was not restricted to any specific construction ('698 Patent: 11:53-55, 63-67).

99. With respect to the claimed "second device," a person of ordinary skill in the art at the time, including myself, would understand that the patent teaches and discloses that the "second device" is a common and ordinary mass spectrometry instrument used by scientists at the time to detect transient signals including, for example, TOF MS, simultaneous or sequential mass analyzers, array-detector magnetic sector, 3D ion trap, linear ion trap, quadrupole devices, and equivalents thereof (*see e.g.*, '698 17:66-18:3 and 18:6-23).

C. "Detect ..." terms (386/'698 Patents)

Claim Term(s)	Fluidigm's Proposed Construction

“detect ... lanthanides and/or noble metals of the single first cell ..., and lanthanides and/or noble metals of the single second cell" '698 Patent	• "detect": Plain and ordinary meaning. • "lanthanides": Lanthanides include any element having atomic numbers 57-71. • "noble metals": Noble metals include any of several metallic elements, the electrochemical potential of which is much more positive than the potential of the standard hydrogen electrode, therefore, an element that resists oxidation. Examples include palladium, silver, iridium, platinum, and gold.
"detecting ... the elemental composition of the first cell"	• Analyzing elements or isotopes of the elemental tags bound to analyte in or on the first cell, by mass spectrometry
"detecting ... the elemental composition of the second cell" '386 Patent	• Analyzing elements or isotopes of elemental tags bound to analyte in or on the second cell, by mass spectrometry

100. I understand that all of the asserted claims of the ‘386 Patent depend from independent Claim 1, and that all of the asserted claims of the ‘698 Patent depend from independent Claim 1.

101. Claim 1 of the ‘386 Patent contains the terms: "detecting ... the elemental composition of the first cell" and "detecting ... the elemental composition of the second

cell." Similarly, Claim 1 of the ‘698 Patent contains the limitation "detect ... lanthanides and/or noble metals of the single first cell ..., and lanthanides and/or noble metals of the single second cell."

102. In my opinion, a person of ordinary skill in the art at the time of the filing of the application for the ‘386 Patent, including myself, would understand that the term "detecting ... the elemental composition of the first cell" and “detecting … the elemental composition of the second cell,” as used in the '386 Patent, mean "*analyzing elements or isotopes of the elemental tags bound to analyte in or on the first cell [or in or on the second cell], by mass spectrometry*."

103. My opinion with respect to the meaning of these terms is based on the language of the terms, my review and understanding of how these terms are used in the claims and specification of the ‘386 Patent, and how a person of ordinary skill in the art at the time would understand them. As discussed above, both the ‘386 and ‘698 Patents are directed to mass spectrometry based multi-parametric particle analysis ('386 and '698 Titles and Abstracts).[4] Further, the '386 Patent describes "measuring the elemental composition of ... a tag or label associated with an analyte located on or in the cell ... by employing the mass-to-charge ratio" ('386 6:11-17), and further discloses that "[t]he elemental composition of the particle or elemental tag is determined by a spectrometer 106 operatively connected to the device 104. Spectrometer 106 may, for example, include a mass spectrometer 106 which detects the ions" ('386 7:56-61). As such, both patents plainly explain and describe detecting elemental compositions of cells by using mass spectrometry methods and techniques to analyze the elemental tags

[4] While I reference portions of the ‘386 Patent in this Report, as the specifications for the ‘386 and ‘698 Patents are identical, the references are applicable to both patents.

that are bound to analyte in or on the first and second cells, by detecting the ions generated from elemental tags.

104. The meaning of these limitations is also supported by the disclosures in both patents that a "tag" is a label, and specifically "a chemical moiety that provides a distinguishable signal of the presence of the analyte or analyte complex with which it is associated" ('386 5:52-54). Both patents explain that the "elemental tag" is a tag that contains an element or an isotope of an element, that provides the distinguishable signal ('386 5: 56-58). Accordingly, a person of ordinary skill in the art at the time would understand from both patents that "detecting ... the elemental composition of the first cell" means that the elements or isotopes of the elemental tags that are bound to analyte in or on the first cell [or in or on the second cell] are analyzed using mass spectrometry.

105. The claim language itself fully supports these constructions. Specifically, the full phrases as recited in Claim 1 of the '386 Patent require "detecting, using mass spectrometry, the elemental composition of the first cell by detecting a transient signal of the multiple vaporized, atomized and ionized elemental tags of the first cell" and "detecting, using mass spectrometry, the elemental composition of the second cell by detecting a transient signal of the multiple vaporized, atomized and ionized elemental tags of the second cell." Thus, the full context of the terms as used in the claim is that the transient signal of the multiple vaporized, atomized and ionized elemental tags is detected in order to detect the elemental composition of the cell (*see also* discussions of terms "transient signal" and "vaporized, atomized and ionized" elsewhere herein). Stated differently, the "elemental composition" that is detected in the method as

claimed, is that resulting from detection of the elemental tag ions (*see, also, e.g.*, '386 10:28-30: "the amount of a tag element detected by the mass spectrometer is proportional to the amount of tagged affinity product bound to the cell").

106. Accordingly, the phrases "detecting ... the elemental composition of the first cell" and "detecting ... the elemental composition of the second cell" as recited in Claim 1 of the '386 Patent would be understood by a person of ordinary skill in the art at the time of the invention, including myself, to mean, respectively, "analyzing elements or isotopes of the elemental tags bound to analyte in or on the first cell, by mass spectrometry," and "analyzing elements or isotopes of the elemental tags bound to analyte in or on the second cell, by mass spectrometry."

107. I reviewed IONpath's proposed construction of these terms, find them to be inaccurate, and do not agree with their proposed definitions (*see* Joint Claim Construction and Prehearing Statement filed June 1, 2020). Specifically, IONpath proposes that the phrases "detecting ... the elemental composition of the first cell" and "detecting ... the elemental composition of the second cell" would be understood by a person of ordinary skill in the art to mean "individually discerning on a cell-by-cell basis ... the elements that make up the first cell" and "individually discerning on a cell-by-cell basis ... the elements that make up the second cell." IONpath's proposed constructions appear to seek to require that “all” of the elements that make up a cell (first cell and second cell) must be detected, not just the ionized elements or isotopes of the *elemental tags* as expressly recited in the claims. For example, IONpath’s proposed constructions, as I understand them, would require that all *endogenous* elements that constitute ("make up") the cell, such as carbon, oxygen, nitrogen,

hydrogen, etc., must be detected. This construction is not supported by the specification, claims, or the claimed inventions.

108. The ‘386 and '698 Patents are directed to, and claim, the detection of the *elemental tags* that are bound to the cells and are not concerned with the detection of other endogenous materials present in the cell. Indeed, the lanthanide and noble metals are used as elemental tags precisely because they are not endogenous to the cell so that they can effectively be used as labels, such that their detection is indicative of the analyte of interest. In my opinion, the reason for this is simple: as understood by those of ordinary skill in the art, the feature of claimed inventions of the ‘386 and ‘698 Patents is that they provide for the detection of individual elements or isotopes of elemental tags that are bound to a specific analyte, and liberated therefrom by the vaporization, atomization, and ionization process, as opposed to requiring the detection of ions or ion fragments of the endogenous analyte itself. This allows for elegant differentiation based on the individual weights of the individual elements or isotopes of the elemental tags, and therefore between the individual analytes tagged by each elemental tag. The inventions and claims are not directed to determining, much less requiring a determination and identification of, endogenous ion fragments, most of which would be composed of the same or similar elements (e.g., proteins and other biomarkers composed primarily of carbon, hydrogen, oxygen and nitrogen), and thus not as readily (if at all) distinguishable from one another. Accordingly, in my opinion, a construction of this term that requires or implies that *all* elements (e.g. including hydrogen, carbon, nitrogen, oxygen) of the cell are somehow measured or detected, as opposed to just those elements or isotopes of the elemental tags (as expressly recited in

the claims), simply does not comport with the claims, specification, described invention, or what a person of ordinary skill in the art would understand. Indeed, that would miss the entire point of these inventions, which is to detect the element tags in order to determine the presence of the analytes, not to determine all elements of the cell.

109. A construction requiring detection of *all elements* (including endogenous materials) in a cell does not comport with the claims or specifications. For example, Claim 1 of the '386 Patent specifically requires "detecting ... the elemental composition of the first cell by *detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the first cell*" (emphasis added). Similarly, Claim 1 of the '698 Patent requires "detecting a transient signal of the multiple vaporized, atomized, and ionized elemental tags of the single [first and second] second cell." As such, the claims expressly set out, as the specification also supports, that the elemental composition is that resulting from the detection of the *ionized elemental tags*, not from the detection of any or all endogenous elements of the cell. Accordingly, in my opinion, IONpath's proposed construction is incorrect, inaccurate, and does not comport with any of the intrinsic evidence. If it were sufficient to detect all the elements of the endogenous material to distinguish between the analytes, then there would be no need for unique tags. Given the technology of 2004, or even of today, it is not possible to uniquely identify analytes in a single cell from analysis of the elements of endogenous material.

110. IONpath's proposed constructions of these terms to include "individually discerning on a cell-by-cell basis ... the elements that make up the first cell" and

"individually discerning on a cell-by-cell basis ... the elements that make up the second cell" seem to try to require that not only every element, i.e. endogenous and exogenous (i.e. elemental tags) are detected, but also that such detection is comprehensive as to every single endogenous and/or exogenous element in the cell. Or in other words, IONpath's proposed constructions would also seem to require *the identification of each and every elemental tag bound to analyte in or on each cell*. A person of ordinary skill in the art having reviewed the '386 and '698 Patents would not understand the claim limitations to require the complete and total identification of every single elemental tag that is tagged to an analyte. Not only do the patents and claims not require such a construction, persons of ordinary skill in the art would understand a complete identification is not claimed, taught, necessary, or even desirable (or possible) in order to obtain information about analyte in or on the cell (*see, e.g.,* '386 10:28-30: "the amount of a tag element detected by the mass spectrometer is proportional to the amount of tagged affinity product bound to the cell").

111. Further, persons of ordinary skill in the art at the time understood the practical limits on the number of ions that can actually be generated from a sample and detected, in any system – which is less than 100% of the total number of bound elemental tags. This is because this would require not only that 100% of the elemental tags be ionized, but also that all of these ionized elemental tags travel to and make it to the detector, when in reality some good number of ions will be lost in any system when traveling between the vaporization, atomization and ionization device and the detector. Accordingly, IONpath's proposal is, in my opinion, wholly divorced from how these systems work and also at odds with the disclosed and claimed invention.

112. Further, with respect to the limitation "detect ... lanthanides and/or noble metals of the single first cell ..., and lanthanides and/or noble metals of the single second cell ..." as recited in Claim 1 of the '698 Patent, my analysis is essentially the same as that for the ‘368 Patent. While the limitation in Claim 1 of the ‘698 Patent is more specific with respect to the detection of "lanthanides and/or noble metals" as compared to the "elemental composition" recited in Claim 1 of the '386 Patent, it is otherwise linguistically the same. This limitation is readily understandable from the claim itself. Specifically, the complete portion of the claim directed to the detection is: "a second device to detect, by mass spectrometry, lanthanides and/or noble metals of the single first cell by detecting a transient signal of the multiple vaporized, atomized and ionized elemental tags of the single first cell, and lanthanides and/or noble metals of the single second cell by detecting a transient signal of the multiple vaporized, atomized and ionized elemental tags of the single second cell." A person of ordinary skill in the art would understand that the "lanthanides and/or noble metals" that are detected with the second device are those resulting from detection of the elemental tag ions (*see, also, e.g.*, '698 10:27-29: "the amount of a tag element detected by the mass spectrometer is proportional to the amount of tagged affinity product bound to the cell").

113. Accordingly, it is my opinion that the limitation means to "analyze lanthanides and/or noble metals of the elemental tags bound to analyte in or on the single second cell, and analyze lanthanides and/or noble metals of the elemental tags bound to analyte in or on the single second cell, by mass spectrometry."

114. Furthermore, the construction IONpath proposes for this limitation is similarly incorrect, namely, "individually discerning on a cell-by-cell basis ... the lanthanides

and/or noble metals that make up the first cell ...individually discerning on a cell-by-cell basis ... the lanthanides and/or noble metals that make up the second cell." In my opinion, IONpath's construction is improper for at least the same reasons expressed above with respect to the analogous limitation for Claim 1 in the '386 patent. Indeed, nothing in the disclosure of the '386/'698 Patents or claims would indicate to a person of ordinary skill in the art that the determination of the *entire lanthanide and/or noble metal make-up* of the cell was necessary, claimed, or required, including the determination of both *any endogenous species* (if present) along with the lanthanides and/or noble metals of the elemental tags. As discussed for the analogous phrases in Claim 1 of the '386 Patent above, these interpretations impose inaccurate and even scientifically incorrect restrictions on the claim term, and thus IONpath's proposed construction is not, in my opinion, a reasonable proposal for the term at issue.

D. "Sequentially" Terms ('386 and '689 Patents)

Claim Term(s)	Fluidigm's Proposed Construction

“detected sequentially" '398/'698 Patents	Observed at separate times
"sequentially analyzing single cells” '386 Patent	Analyzing single cells at separate times
“sequentially analyzing single cells in a sample” '698 Patent	Analyzing single cells in a sample separately, not at the same time

115. I understand that dependent Claims 6, 9-10 and 18-19 of the '386 Patent, and Claims 5 and 6 of the '698 Patent, are involved in the subject lawsuit (“’386/’698 Asserted Claims”), that these claims each depend from an independent Claim 1, and the corresponding Claim 1 recites the term “detected sequentially” (‘386/'698 Patent), and either the term "sequentially analyzing single cells" ('386 Patent) or "sequentially analyzing single cells in a sample" ('698 Patent).

116. In my opinion, a person of ordinary skill in the art at the time of the filing of the application which resulted in the ‘386 and '698 Patents would understand that the term “detected sequentially,” as used in the subject claims, specification, and file history, means “*observed at separate times.*” Similarly, it is my opinion that a person of ordinary skill in the art at the time of the filing of the application which resulted in the

‘386 and '698 Patents, including myself, would understand that the preamble terms "sequentially analyzing single cells" and "sequentially analyzing single cells in a sample," mean "*analyzing single cells at separate times*" and "*analyzing single cells in a sample separately, not at the same time*," respectively.

117. My opinion with respect to the meaning of these terms is based on my review and understanding of how these terms are used in the claims and specification of the ‘386 Patent, and how a person of ordinary skill in the art at the time would understand them. As discussed above, both the ‘386 and ‘698 Patents are directed to mass spectrometry based multi-parametric particle analysis ('386 and '698 Titles and Abstracts) (again, while I reference portions of the ‘386 Patent in this Report, as the specifications for the ‘386 and ‘698 Patents are identical, the references are applicable to both patents), including analysis of single particles such as single cells ('386: 1:33-35). The '386 Patent describes "apparatus and methods for sequentially analyzing particles, for example single cells or single beads, by spectrometry" ('386: 1: 33-36), and further describes "introducing particles sequentially and analyzing the particles (for example, single particles such as single cells or single beads), by spectrometry" ('386: 2:55-58). As such, the '386 and '698 Patents clearly describe analysis being performed at different times with respect to different particles of cells, such as according to different sequences of analysis (e.g. analysis with respect to a first cell at a first time, and analysis with respect to a second cell at a second time). This is in contrast to analyzing particles of all of the cells at the same time (i.e. an aggregate cell analysis) in which case individual information with respect to each cell would be subsumed into the aggregate information, resulting in loss of information on the single cell level.

Performing the analysis of the particles of cells separately, and not at the same time, allows for individual analysis with respect to each cell, e.g. identification of analyte in or on each analyzed cell, for example by detecting transient signals of ionized elemental tags with respect to each cell. That is, an analysis at the single cell level can be achieved by separately performing analysis with respect to each call, at different times, to distinguish the analysis for each cell from that of other cells.

118. Accordingly, in my opinion, a person of ordinary skill in the art would understand the phrase "detected sequentially," with respect to detection of transient signals for analysis of particles associated with the single cells using mass spectrometry in the '386 and '698 Patents, to simply mean that the transient signals are "observed at different times" to provide the separate analysis with respect to the individual cells, as opposed to an aggregate analysis of all cells at the same time.

119. My understanding of the meaning of the phrase "detected sequentially" is further informed by the use of the phrase "detected sequentially" as used in the context in claim 1 in both the '386 and '698 Patents. In the '386 Patent, this phrase appears as a part of the recitation "*detecting*, using mass spectrometry, the elemental composition of *the first cell* by *detecting a transient signal* of the multiple vaporized, atomized and ionized elemental tags *of the first cell* ... and *detecting*, using mass spectrometry, the elemental composition of *the second cell* by *detecting a transient signal* of the multiple vaporized, atomized and ionized elemental tags of the *second cell*, *wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially*." Here, the analysis involves detecting transient signals associated with each respective cell, at different points in time from

one another, to provide for individual analysis with respect to each cell. In plain language, the transient signals corresponding to each cell are *observed at separate times*, in order to provide analysis on the single cell level (specifically, analysis of ionized elemental tags from each cell), as opposed to a simultaneous analysis of a cell aggregate. Similarly, the '698 Patent recites "wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially," and so "detected sequentially" as used in this phrase, as with the '386 Patent above, would be understood by one of ordinary skill in the art to mean that the transient signals are *observed at separate times*, not at the same time, to provide for the single cell analysis.

120. As noted above, I am not a patent attorney, or an expert in patent law, and provide no opinion as to whether the phrases "sequentially analyzing single cells" and " sequentially analyzing single cells in a sample" should be considered limitations of the claim, since these terms appear in the preamble and do not appear in the body of the claim. Nonetheless, I do have an opinion as to the meaning a person of ordinary skill in the art would give to these terms. Specifically, in light of the '386 and '698's disclosure of providing apparatus and methods for the analysis of cell at the single cell level, I believe a person of ordinary skill in the art would understand the phrase "sequentially analyzing single cells" ('386 Patent) to simply mean "*analyzing single cells at separate times*," and would understand "sequentially analyzing single cells in a sample" ('698 Patent) to mean "*analyzing single cells in a sample separately, not at the same time*," to provide for analysis of cells on the single cell level, as discussed for the term "detected sequentially" above.

121. I have also reviewed IONpath's proposed constructions for the terms "sequentially analyzing single cells," and "sequentially analyzing single cells in a sample," and I am of the opinion that their proposed constructions are incorrect. I also note that IONpath declined to provide a construction for the term "detected sequentially," stating instead that the term "sequentially" "should be understood in the context of the surrounding language ..." (*see* page 15 of Exhibit 1 to Joint Pre-Hearing Statement filed on June 10, 2020). Accordingly, I am uncertain as to what construction IONpath intends to propose for the term "detected sequentially" and am currently unable to provide any opinion in this regard.

122. However, with respect to the term "sequentially analyzing single cells" ('386 Patent), I understand that IONpath proposes the construction "individually discerning elemental composition on a cell-by-cell basis" (*see* page 15 of Exhibit 1 to Joint Pre-Hearing Statement filed on June 10, 2020). In my opinion, this proposed construction is at best flawed, and at worst misleading, particularly as read in conjunction with IONpath's proposed constructions for the "detect ..." terms discussed in Section C above. Specifically, I note that IONpath proposes construing "detecting ... the elemental composition of the first [or second] cell" to mean "individually discerning on a cell-by-cell basis ... the elements that make up the first [or second] cell." As discussed above, I believe one of ordinary skill in the art would not understand this "detect .." term in the '386 Patent (or the similar "detect ..." term in the '698 Patent) to have this meaning, as it seems to imply that *all types of elements* (i.e. not only elemental tags, but also any endogenous elements such as carbon, hydrogen, oxygen) have to be identified for each cell that is analyzed, and/or that *each and every one of*

such elements (whether endogenous or exogenous) that "make up" the cell would have to be identified. As I have expressed above, I believe such an interpretation is inconsistent with the invention as disclosed of the '386 and '698 Specifications, and also inconsistent with the terms as used in the claims. The claimed invention is clearly directed to the detection of the *ionized metal tags* from the cells, and not every single element, endogenous or otherwise, present in the cell. Likewise, the claims of the '386 and '698 Patent do not require that *every single element that might be present in a cell*, endogenous or otherwise, be determined, and instead one of ordinary skill in the art would appreciate that information is obtained just from those elemental tags that are vaporized, atomized and ionized *from* the cells (*see, e.g.,* "vaporizing, atomizing, and ionizing multiple elemental tags from a single first [second] cell" in '386 and "vaporize, atomize and ionize multiple elemental tags from a single first [second] cell" in '698), to provide for the single cell analysis and system as described in the '386 and '698 Patents.

123. Accordingly, to the extent that IONpath's proposed construction for "sequentially analyzing single cells" references IONpath's proposal for the "detect ..." terms, I am of the opinion that IONpath's proposed construction is not correct. Specifically, IONpath proposes the construction "individually discerning elemental composition on a cell-by-cell basis," where "elemental composition" as used here is presumably intended to be interpreted in a manner consistent with IONPath's construction in the "detect ..." terms of Section C above, and namely as meaning "... the elements that make up the first [second] cell." As discussed above, this construction would seem to imply that sequentially analyzing single cells also requires determination of *every single one of each type of* elements (endogenous or otherwise)

that "make up" the cell, and thus this construction is in my opinion incorrect. In my opinion, there is nothing in the '386 or '698 Patent claims or disclosures that would indicate to one of ordinary skill in the art that the sequential analysis of single cells described therein was intended to be limited to only those techniques capable of determining *every single one of each type of element* present in the cells, as would be inferred from IONpath's proposed construction. Similarly with respect to IONPath's proposed construction for the analogous term in the '698 Patent, namely "sequentially analyzing single cells in a sample," I am of the opinion that, to the extent this construction relies on IONpath's construction for the "detect ..." terms in Section C, it imposes limitations that do not have any basis in the '386/'698 specifications or claims, and so is not a correct construction for this term.

124. Furthermore, I note that if IONPath intends the phrase "on a cell-by-cell basis" that forms a part of their proposed construction of "sequentially analyzing single cells in a sample" to simply mean that a single cell analysis, or analysis on the individual cell level, is being performed, I would not necessarily disagree to at least this portion of the proposed construction. However, if IONpath intends "on a cell-by-cell basis" to be read in conjunction with the "detect ..." terms of Section C above to mean that *everything* (i.e. all elements, endogenous or exogenous, and every single one of such elements) is determined for a first cell, *before* a second cell can even be analyzed, I would have to disagree with this proposal, as it is my opinion that the phrases "sequentially analyzing single cells" and "sequentially analyzing single cells in a sample" do not require the type of comprehensive analysis with respect to each and every element and/or elemental tag in each cell, that is being implied by IONpath's

proposal I further note that if IONpath's intent is to mean that every atom of each element in the sample is detected and counted, that is not what the claim would mean to a person of ordinary skill in the art as, indeed, it would not be a practicable approach. Mass spectrometry systems today and in 2004 are not capable of such extensive data collection. Note that there are over 10 trillion atoms in a single typical mammalian cell.

E. "Transient" Terms ('386 and '689 Patents)

Claim Term(s)	Fluidigm's Proposed Construction
"transient signal" '398/'698 Patents	The detectable ions generated for a limited duration of time
"detecting ... wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially" '386 Patent	Each of the disputed claim terms given its construction (as identified herein): "detecting": plain and ordinary meaning. "transient signal": the detectable ions generated for a limited duration of time. "detected sequentially": observed at separate times (see also Section D above).
"detecting ... wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially"	Each of the disputed claim terms given its construction (as identified herein): "detecting": plain and ordinary meaning. "transient signal": the detectable ions generated for a limited duration of time. "detected sequentially": observed at separate times (see also Section D above).

'698 Patent	

125. I understand that dependent Claims 6, 9-10 and 18-19 of the '386 Patent, and Claims 5 and 6 of the '698 Patent, are involved in the subject lawsuit ("'386/'698 Asserted Claims"), that these claims each depend from an independent Claim 1, and the corresponding Claim 1 recites the term "transient signal" ('386/'698 Patent), and either the term "detecting ... wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially" ('386 Patent) or " detecting ... wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially"

126. In my opinion, a person of ordinary skill in the art at the time of the filing of the application which resulted in the '386 and '698 Patents would understand that the term "transient signal," as used in the subject claims, specification, and file history, means "*the detectable ions generated for a limited duration of time.*" Similarly, it is my opinion that a person of ordinary skill in the art at the time of the filing of the application which resulted in the '386 and '698 Patents would understand that the terms "detecting ... wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially" and " detecting ... wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially," when incorporating the above definition of "transient signal" therein, simply mean "*detecting ... wherein the detectable ions generated for a limited duration of time associated with the first cell and the detectable ions generated for a limited duration of time associated with the*

second cell are detected sequentially" and "*detecting ... wherein the detectable ions generated for a limited duration of time associated with the single first cell and the detectable ions generated for a limited duration of time associated with the single second cell are detected sequentially,"* respectively.

127. My opinion with respect to the meaning of these terms is based on my review and understanding of how these terms are used in the ‘386 Patent, and how a person of ordinary skill in the art at the time would understand them. As discussed above, both the ‘386 and ‘698 Patents are directed to mass spectrometry based multi-parametric particle analysis ('386 and '698 Titles and Abstracts) (again, while I reference portions of the ‘386 Patent in this Report, as the specifications for the ‘386 and ‘698 Patents are identical, the references are applicable to both patents). As discussed in the Background section above, as well as with respect to the "vaporization, atomization and ionization" terms in Section A, the '386 and '698 Patents describe vaporizing, atomizing and ionizing multiple elemental tags, to provide ionized atomic components suitable for detection by mass spectrometry.

128. With respect to this detection of the ionized atomic components, the '386 Patent describes detecting transient signals that arise as a part of this vaporization, atomization and ionization process. For example, '386 discloses detecting transient signals where "in the instance of the use of an ICP as the vaporizer, atomizer and ionizer, the transient signals from a single particle may last for a period in the range of 20 to 200 microseconds" ('386: 18:8-10). In other words, '386 discloses that the vaporization, atomization and ionization of the elemental tags from a cell can provide a transient signal of the ionized atomic components of the elemental tags, for a limited duration of time.

'386 further discloses that a TOF analyzer can be used, which "samples a packet of ions in a given time period ... [and] is suited to the analysis of short transients such as those produced by single particles ..." ('386: 18:49-55). Accordingly, in my opinion, the '386 and '698 claims and specifications describe transient signals corresponding to the detectable ions, and further describe that such signals are of limited duration in time. Therefore, it is my opinion that the phrase "transient signal" can be understood as "the detectable ions generated for a limited duration of time."

129. My review of the prosecution history of the '386 Patent further confirms this construction. Specifically, I refer to the Amendment filed (hereinafter referred to as the "Amendment") during prosecution of the '386 Patent on September 18, 2018, which led to allowance of the case shortly thereafter on October 25, 2018. In this Amendment, the prosecuting attorney wrote with respect to U.S. PG-Pub No. 2002/0086441 to Baranov (hereinafter referred to as "Baranov '441"), that "[a]dditionally, the cited portions of Baranov are silent with respect to any benefits of detecting element tags in individual cells, as well as how to analyze multiple elemental tags from a single cell before the transient signal disappears" (page 8 of Amendment). In other words, the prosecution history of the '386 Patent supports the proposed construction of "the detectable ions generated for a limited duration of time," because it indicates that the multiple elemental tags (i.e. the ionized atomic components thereof) from a single cell are analyzed before the transient disappears, or in other words that the detectable ions corresponding to the vaporized, atomized and ionized multiple elemental tags are of limited duration.

130. Furthermore, with respect to the longer terms incorporating "transient signal," namely "detecting ... wherein the transient signal associated with the first cell and the

transient signal associated with the second cell are detected sequentially" and " detecting ... wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially," I am of the opinion that these terms would be understood by one of ordinary skill in the art by inserting the proposed construction for "transient signal" therein to mean "*detecting ... wherein the detectable ions generated for a limited duration of time associated with the first cell and the detectable ions generated for a limited duration of time associated with the second cell are detected sequentially*" and "*detecting ... wherein the detectable ions generated for a limited duration of time associated with the single first cell and the detectable ions generated for a limited duration of time associated with the single second cell are detected sequentially,"* respectively. As they appear in these phrases, the terms "detected sequentially" in my opinion would be understood as "observed at separate times" as discussed in further detail above in Section C, and the term "detecting" would simply be understood according to it plain and ordinary meaning to a person of ordinary skill in the art.

131. I have also reviewed IONpath's proposed construction for these phrases "detecting ... wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially"('386 Patent) and " detecting ... wherein the transient signal associated with the single first cell and the transient signal associated with the single second cell are detected sequentially" ('698 Patent). I note that I was unable to ascertain IONpath's proposed construction for the term "transient signal," as IONpath declined to provide any proposed construction at all for this term, and instead simply referred to the longer terms that incorporate the phrase "transient signal" therein

for their constructions (*see*, page 23 of Joint Pre-Hearing Statement filed on June 1, 2020).

132. With respect to these phrases that IONpath provided proposed definitions, I disagree with IONpath's proposed constructions as it is unclear to me what is meant by "detecting the individual signal of an individual cell event for the first cell, and detecting the individual signal of an individual cell event for the second cell" (the construction for both the '386 and '698 phrases). In particular, it is not clear to me what is meant by "individual signal of an individual cell event" in this phrase, and how this is intended to fit into the longer phrase of, for example in '386, " detecting ... wherein the transient signal associated with the first cell and the transient signal associated with the second cell are detected sequentially." For example, it is unclear if this phrase is intended to refer only to detecting the transient signals associated with the first and second cells, or whether it is also intended to construe the "detected sequentially" part of this phrase. As discussed in Section C above, the phrase "detected sequentially" would be understood by a person of ordinary skill in the art to mean "observed at separate times," whereas IONpath's proposed construction does not indicate whether the transient signals are detected simultaneously, or separately from one another. Accordingly, since IONpath's proposed construction does not clearly and fully account for all of the features of the claimed phrase, it is my opinion that one of ordinary skill in the art would not have found the subject phrases to have the meaning as proposed by IONpath.

133. Furthermore, I note that IONPath's proposed phrase of "detecting the individual signal of an individual cell event," if intended simply to refer to detecting transient ions created by vaporization, atomization and ionization of elemental tags from a cell, is not

necessarily inconsistent with my understanding of "transient signal" as used in the '386 and '698 claims. That is, if the "cell event" referred to by IONpath is the vaporization, atomization and ionization of the elemental tags from a cell (such as for example a "cell event" corresponding to vaporization, atomization and ionization in an ICP plasma, or a "cell event" corresponding to the directing of an ion beam onto a cell in a tissue sample), and the "individual signal" referred to by IONpath are those detectable ions of limited duration associated with each cell, then IONpath's construction would seem to be consistent with "detecting ... [wherein] the detectable ions of limited duration associated with the single first cell [second cell] and the detectable ions of limited duration associated with the single second cell," similarly to Fluidigm's proposed construction. However, since I cannot ascertain with any certainty how IONpath is construing the terms "individual signal" and "individual cell event" or how IONpath intends the term "detected sequentially" to be understood in this phrase (another term that IONpath declined to construe, see Section C above), my conclusion is that one of ordinary skill in the art would not understand the subject phrase to have the meaning proposed by IONpath's, as it is ultimately unclear what construction exactly IONpath intends.

F. "Lanthanide" Terms ('386 and '689 Patents)

Claim Term(s)	Fluidigm's Proposed Construction
"lanthanide or noble metal" '398/'698 Patents "lanthanides and/or noble metals"	Lanthanides include any element having atomic numbers 57-71 Noble metals include any of several metallic elements, the electrochemical potential of which is much more positive than the potential of the standard hydrogen electrode, therefore, an element that resists oxidation. Examples include palladium, silver, iridium, platinum and gold.

'698 Patent	

134. I understand that dependent Claims 6, 9-10 and 18-19 of the '386 Patent, and Claims 5 and 6 of the '698 Patent, are involved in the subject lawsuit ("'386/'698 Asserted Claims"), that these claims each depend from an independent Claim 1, and the corresponding Claim 1 recites the term "lanthanide or noble metal" ('386/'698 Patent), with claim 1 of the '698 Patent also reciting the term "lanthanides and/or noble metals."

135. In my opinion, a person of ordinary skill in the art at the time of the filing of the application which resulted in the '386 and '698 Patents would understand that the term "lanthanide," as used in the subject claims, specification, and file history, includes "*any element having atomic numbers 57-71*." Similarly, it is my opinion that a person of ordinary skill in the art at the time of the filing of the application which resulted in the '386 and '698 Patents would understand that the term "noble metal" includes "any of several metallic elements, the electrochemical potential of which is much more positive than the potential of the standard hydrogen electrode, therefore, an element that resists oxidation. Examples include palladium, silver, iridium, platinum and gold".

136. My opinion with respect to the meaning of these terms is based on my review and understanding of how these terms are used in the claims and specifications of the '386 and '698 Patents, and how a person of ordinary skill in the art at the time would

understand them. Specifically, referring to the '386 Specification, I note that U.S. Patent Application Serial No. 09/905,907 (Baranov '441) is referred to with respect to the tagging of biologically active materials ('386: 9: 16-18) (again, while I reference portions of the ‘386 Patent in this Report, as the specifications for the ‘386 and ‘698 Patents are identical, the references are applicable to both patents). Reviewing the relevant portions of the Baranov '441 Specification, I find the disclosure with respect to lanthanides that "[l]anthanides include any element having atomic numbers 58-71" (Baranov '441: paragraph [0070]). While this is consistent with the disclosure in the '386 Specification (*see, e.g.*, '386: 10:4-8 "there are as mentioned at least 35 isotopes of the lanthanides and noble metals alone that may be obtained in enriched form"), I also find that the '386 Specification uses the element Lanthanum, which corresponds to element 57 (*see, e.g.*, '386: 9: 58-60 "the tags can be constructed using the natural isotopic distributions of, for example ... La, Ce, Pr, Nd, Sm, Eu, Th, Dy, Ho, Er, Tm, Yb, Lu ...). Accordingly, my understanding from my review of the '386 and '698 Patents, including the Baranov '441 application referred to therein, leads me to believe that by "lanthanide" what is meant in the claim terms is "any element having atomic numbers 57-71." This definition is also consistent with my understanding as a person of ordinary skill in the art of the term "lanthanides."

137. Similarly, with respect to "noble metals," the Baranov '441 application referred to in the '386 Patent with respect to the tagging of biologically active materials ('386: 9: 16-18), discloses that "noble metals include any of several metallic elements, the electrochemical potential of which is much more positive than the potential of the standard hydrogen electrode, therefore, an element that resists oxidation. Examples

include palladium, silver, iridium, platinum and gold" (Baranov '441, paragraph [0075]). This definition is also consistent with my understanding as a person of ordinary skill in the art of the term "noble metal." Accordingly, as I do not find any definition of "noble metal" in the '386/'698 Patents that is in any way in conflict with this definition, and since Baranov '441 is referred to with respect to tagging in the '386 and '698 Patents, I believe that one of ordinary skill in the art would understand the term "noble metal" to have this same meaning as set forth in the Baranov '441 application.

138. I have also reviewed IONpath's proposed construction for "lanthanides" and "noble metals," and I do not believe that a person of ordinary skill in the art would understand these terms to have the meaning ascribed to them by IONpath. Specifically, IONpath proposes that the phrase "lanthanide or noble metal" should be construed as meaning "element, isotope, ion and/or composition comprising element with atomic number 57-71, ruthenium, rhodium, palladium, silver, indium, hafnium, rhenium, iridium, platinum, gold, ruthenium, copper, osmium, mercury or nickel," which, in my opinion, encompasses more elements and materials than can reasonably be construed to be a "lanthanide" or a "noble metal".

139. Referring to the first part of the proposed construction, which presumably is intended to cover "lanthanides," I note that the proposed construction properly recites elements of atomic number 57-71. However, the proposed construction also indicates that a lanthanide is any "element, isotope, ion and/or composition" comprising this atomic number. Lanthanides are elements, and can be provided in the form of isotopes, and as discussed with respect to vaporization, ionization and atomization, lanthanide ions can also be provided. However, I am uncertain what IONpath means by a

lanthanide "composition" here. Specifically, I am not certain whether this is intended to imply that some ionized structure larger than just the lanthanide element itself is detected by mass spectrometry in the claimed method and system, which would be inconsistent with the disclosure in '386 and '698 Patents of using mass spectrometry to mass differentiate between different lanthanides and/or noble metals themselves, that are used as elemental tags.

140. With respect to the second part of the proposed construction, I believe that the elements referred to therein go beyond what would be understood by a person of ordinary skill in the art to be a "noble metal" and in light of the definition thereof in the Baranov '441 application that the '386 and '698 Patents refer to. For example, indium and nickel are examples of elements that would not be understood by a person of ordinary skill in the art to be a noble metal (or a lanthanide for that matter). Furthermore, copper has an electrochemical potential that is much lower than the noble metals palladium, silver, iridium, platinum and gold that are referred to in the intrinsic record. Furthermore, this proposed construction makes even less sense in light of the disclosure of the '386 and '698 Patents, because one of ordinary skill in the art would understand that certain elements in the list of noble metals proposed by IONpath could be endogenously present in biological materials, such as nickel and copper. In contrast, the '386 and '698 Patents disclose that the elemental tags selected for use with the invention are those that are "not[e] expected to be common in biological systems" ('386: 10: 7-9), presumably so that the detection of the elemental tags can be performed without interference from endogenous material of the same element type. Accordingly, in my opinion, not only would a person of ordinary skill understand that certain of the

elements listed by IONpath were not noble metals, such as indium, copper, or nickel, but one of ordinary skill in the art would also understand that the use of such elements, which might also be endogenously present in a biological sample to be analyzed, would be contrary to the disclosure of the '386 and '698 Patents. Finally, IONpath's proposed construction with respect to "noble metal" suffers from the same deficiency as the proposed construction of "lanthanides," in that the proposed construction includes "compositions" of noble metals, which one of ordinary skill in the art would recognize as being confusing and an inaccurate description of the noble metal elements provided as elemental tags in the invention.

G. "Distinct Isotope" ('386 and '689 Patents)

Claim Term(s)	Fluidigm's Proposed Construction
"distinct isotope" '398/'698 Patents	An isotope of an element that has a distinguishable mass from other isotopes, of the same or other element, used as tags in that sample.

141. I understand that dependent Claims 6, 9-10 and 18-19 of the '386 Patent, and Claims 5 and 6 of the '698 Patent, are involved in the subject lawsuit ("'386/'698 Asserted Claims"). I also understand that claim 9 of the '386 Patent, and claim 6 of the '698 Patent recite the term "distinct isotope" ('386/'698 Patent), with claim 1 of the '698 Patent also reciting the term "lanthanides and/or noble metals."

142. In my opinion, a person of ordinary skill in the art at the time of the filing of the application which resulted in the ‘386 and '698 Patents would understand that the term “distinct isotope,” as used in the subject claims, specification, and file history, means “an isotope of an element that has a distinguishable mass from other isotopes, of the same or other element, used as tags in that sample.”

143. My opinion with respect to the meaning of these terms is based on my review and understanding of how these terms are used in the ‘386 and '698 Patents, and how a person of ordinary skill in the art at the time would understand them. As discussed in the Background section above, the '386 and '698 Patents are directed to multiplex analysis of cell samples, or in other words the ability to simultaneously identify multiple different analytes in a cell sample -- by using elemental tags that act as labels for the different analytes and which provide a distinguishable signal of the presence of analyte or analyte complex with which the elemental tags are associated (*see, e.g.,* '386 Patent 5:52-67). The elemental tags in turn contain an element, or an isotope of an element, that provides the distinguishable signal (*see, e.g.,* '386 Patent, 5:52-67 "the tag (which is also called an "elemental tag") can contain an element or an isotope ... that provide[s] the distinguishable signal"). Specifically, in claim 1 of each of the '386 and '698 Patents, the elemental tags comprise "a lanthanide or noble metal," which can include distinct isotopes thereof, that provides the distinguishable signal corresponding to each of the plurality of tagged antibodies that are tagged with the elemental tags, and which are specific for different analyte in the sample.

144. Accordingly, my understanding from review of the '386 and '698 Patents is that multiplexing can be provided by including elements, or distinct isotopes of elements,

where the distinct isotopes each have a distinguishable mass from other isotopes, of the same or other element, used as tags in the sample (*see, e.g.,* '386 Patent, 5:52-57). To clarify, while different chemical elements have different masses that are distinguishable from one another, due to the combined weights of the protons, neutrons and electrons making up each chemical element, each chemical element can also exist in multiple different isotopic forms according to varying numbers of neutrons present in the nucleus of each. That is, different isotopes of the same element have the same number of protons and electrons, but differ in the number of neutrons present for each isotope, which results in a small -- but detectable -- difference in mass between different isotopes of a same chemical element.

145. My understanding of the term "distinct isotope" as used in the '386 and '698 Patents is further confirmed by the disclosure therein that the use of isotopes can expand the multiplexing options for labelling with the elemental tags (*see, e.g.,* '386 Patent, 5:52-57; 8:17-25 of '386 "a large number of distinguishable element and isotopes can be used as tags"; 9:24-36; 9:56-57 "the tags can be conveniently constructed using the natural isotopic distributions"; 9:67-10:9 of '386 "Where a higher order of multiplexing is desired, the use of commercially-available enriched isotopes .. offers a possibility"). Accordingly, my understanding is that the elemental tags used to tag different antibodies in the '386 and '698 patents can comprise isotopes of the same or other elements, as long as the masses of the isotopes used to tag each antibody are distinguishable from one another to allow for separate identification thereof by mass spectrometry. In other words, I believe that one of ordinary skill in the art would understand "distinct isotope" in the context of claim 9 of the '386 Patent and claim 6 of

the '698 Patent to mean "*an isotope of an element that has a distinguishable mass from other isotopes, of the same or other element, used as tags in that sample*."

146. I understand that IONpath proposes that the term "distinct isotope" be given its plain and ordinary meaning. I believe the construction proposed herein is consistent with the plain and ordinary meaning, but I also note for clarity that the '386 and '698 Patents further describe (and claim) such distinct isotopes in the context of their use in elemental tags, as discussed above, and as such describe that the isotopes used to tag different antibodies can be isotopes of the same or different element, with a mass that is distinguishable from other isotopes used in the sample. This usage is consistent with plain and ordinary meaning.

H. "Pretreating ..." term ('386 Patent)

Claim Term(s)	Fluidigm's Proposed Construction
"pretreating the multiple vaporized, atomized and ionized elemental tags of the first cell occurs in a vacuum" '398 Patent	Conditioning a group of element tag ions in a vacuum and transporting to the mass spectrometer

147. I understand that dependent Claims 6, 9-10 and 18-19 of the '386 Patent, and Claims 5 and 6 of the '698 Patent, are involved in the subject lawsuit ("'386/'698 Asserted Claims"). I also understand that claim 18 of the '386 Patent recites the term "pretreating the multiple vaporized, atomized and ionized elemental tags of the first cell occurs in a vacuum."

148. In my opinion, a person of ordinary skill in the art at the time of the filing of the application which resulted in the '386 Patent would understand that the term "pretreating the multiple vaporized, atomized and ionized elemental tags of the first cell occurs in a vacuum," as used in the subject claims, specification, and file history, means "conditioning a group of element tag ions in a vacuum and transporting to the mass spectrometer."

149. My opinion with respect to the meaning of these terms is based on my review and understanding of how these terms are used in the '386 Patent, and how a person of ordinary skill in the art at the time would understand them. Specifically, I note that the '386 Specification describes providing an ion pretreatment system that transports ions generated by the vaporization, atomization and ionization process to a mass analyzer ('386 3: 18-30 "[t]he instrument has an ion pretreatment system and a mass analyzer. The ion pretreatment system is adapted to transport ions generated by the ionization system to the mass analyzer"). The '386 Specification further describes that the ion pretreatment device can be used to condition the ions for the mass analyzer ('386: 14: 7-11 "an ion pretreatment device 112 may be used to condition the ions for the mass analyzer"). For example, the '386 Patent describes that pretreatment device can comprise a high pass filter ('386: 8: 7-10), such as a high pass filter downstream of a

vacuum interface ('386: 15: 33-34). As yet another example, the '386 Patent describes that a pretreatment device for a TOF mass spectrometer "conditions the ion flow for the needs of the TOF mass analyzer" ('386: 7: 10-14).

150. Accordingly, based on the disclosure in the '386 Specification, I believe one of ordinary skill in the art would understand the phrase "pretreating the multiple vaporized, atomized and ionized elemental tags of the first cell occurs in a vacuum," as used in claim 18 of the '386 Patent, to mean "*conditioning a group of element tag ions in a vacuum and transporting to the mass spectrometer*."

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on: July 16, 2020

Date

Thomas F. Kelly

Thomas F. Kelly